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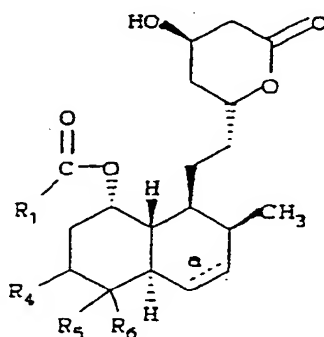
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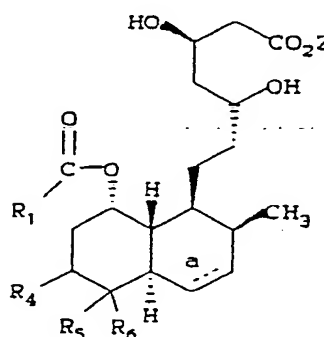
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㉙ 5-oxygenated HMG-CoA reductase inhibitors.

㉚ Novel HMG-CoA reductase inhibitors are useful as antihypercholesterolemic agents and are represented by structural formulae (I) or (II):



(I)



(II)

wherein position 5 of the polyhydronaphthyl ring is singly or doubly bonded to oxygen or incorporated into a C₃₋₇ carbocyclic ring.

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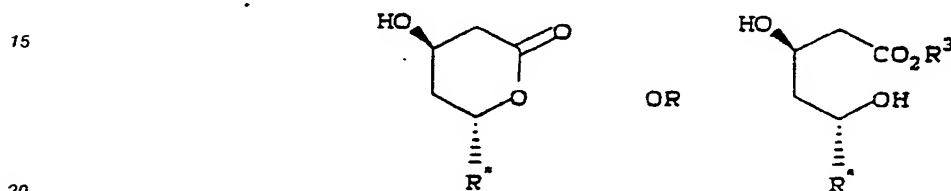
5-OXYGENATED HMG-CoA REDUCTASE INHIBITORS

BACKGROUND OF THE INVENTION

Hypercholesterolemia is known to be one of the prime risk factors for ischemic cardiovascular disease, such as arteriosclerosis. Bile acid sequestrants have been used to treat this condition; they seem to be moderately effective but they must be consumed in large quantities, i.e. several grams at a time and they are not very palatable.

MEVACOR® (lovastatin), now commercially available, is one of a group of very active antihypercholesterolemic agents that function by limiting cholesterol biosynthesis by inhibiting the enzyme, HMG-CoA reductase. In addition to the natural fermentation products, mevastatin and lovastatin, there are a variety of semi-synthetic and totally synthetic analogs thereof.

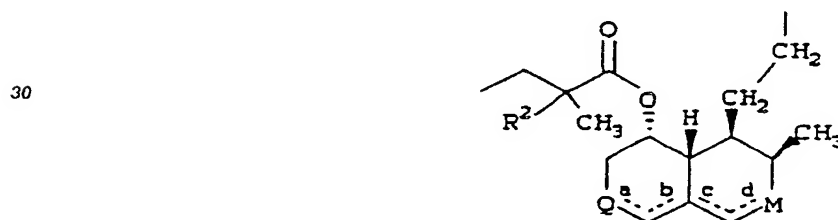
The naturally occurring compounds and their semi-synthetic analogs have the following general structural formulae:



wherein:

R³ is hydrogen, C₁₋₅ alkyl or C₁₋₅ alkyl substituted with a member of the group consisting of phenyl, dimethylamino, or acetylamino; and

R* is



wherein Q is



or

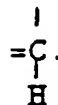
45 R⁵ - C H; R⁵ is H or OH; M is

- C HR⁶, R⁶ is hydrogen or hydroxy;

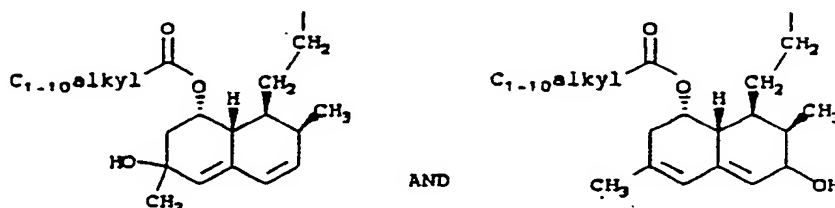
R² is hydrogen or methyl; and a, b, c, and d represent single bonds, one of a, b, c or d represents a double bond, or both a and c or both b and d represent double bonds provided that when a is a double bond, Q is



or

and when \underline{d} is a double bond, M is

U.S. Patent 4,517,373 discloses semi-synthetic hydroxy containing compounds represented by the above general formula wherein R* is

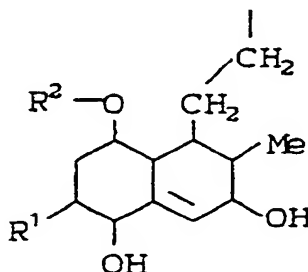


U.S. Patent 4,537,859 and U.S. Patent 4,448,979 also discloses semi-synthetic hydroxy-containing compounds represented by the above general formula wherein R* is



These compounds are prepared by the action of certain microorganisms on the corresponding non-hydroxylated substrates. One such organism described in U.S. 4,537,859 is of the genus *Nocardia*.

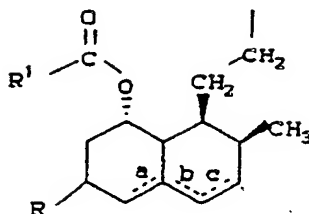
U.K. Patent 2,075,013 discloses semi-synthetic hydroxy containing compounds represented by the above general formula wherein R* is:



wherein R¹ is H or Me, and R² is H or acyl.

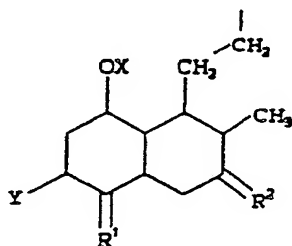
U.S. Patent Application Serial No. 048,136 filed May 15, 1987 discloses 6-substituted compounds of the

above general formula wherein R* is:



wherein R is CH₂OH,

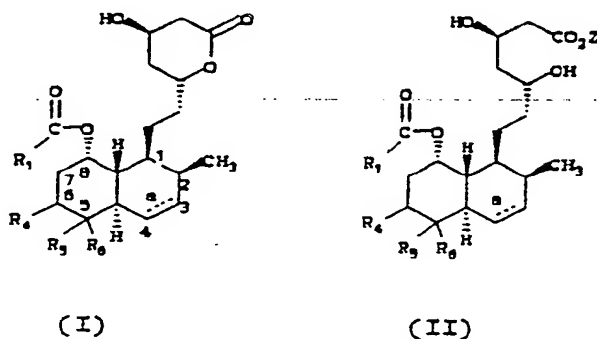
CH₂O-C(=O)-R⁴, CO₂R⁷ or C(=O)-NR⁸R⁹; and R¹, R⁴, R⁷, R⁸ and R⁹ are broadly defined organic moieties.
U.S. Patents 4,604,472 and 4,733,003 disclose compounds of the above formula wherein R* is:



wherein X represents a hydrogen atom or a 2-methylbutyryl group, Y represents a hydrogen atom or a methyl group and R¹ and R² are the same or different and each represents an oxygen atom or a group of formula =N-OR³ where R³ is a hydrogen or alkyl moiety.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to HMG-CoA reductase inhibitors of formulae (I) and (II):



(Numbering relates to positions in tetrahydronaphthyl ring).

wherein:

R₁ is selected from:

(1) C₁₋₁₀ alkyl;

(2) substituted C₁₋₁₀ alkyl in which one or more substituent(s) is selected from

(a) halogen,

(b) hydroxy,

(c) C₁₋₁₀ alkoxy,

- (d) C₁₋₅ alkoxycarbonyl,
- (e) C₁₋₅ acyloxy,
- (f) C₃₋₈ cycloalkyl,
- (g) phenyl,
- 5 (h) substituted phenyl in which the substituents are X and Y,
- (i) C₁₋₁₀ alkylS(O)_n in which n is 0 to 2,
- (j) C₃₋₈ cycloalkylS(O)_n,
- (k) phenylS(O)_n,
- (l) substituted phenylS(O)_n in which the substituents are X and Y, and
- 10 (m) oxo;
- (3) C₁₋₁₀ alkoxy;
- (4) C₂₋₁₀ alkenyl;
- (5) C₃₋₈ cycloalkyl;
- (6) substituted C₃₋₈ cycloalkyl in which one substituent is selected from
- 15 (a) C₁₋₁₀ alkyl
- (b) substituted C₁₋₁₀ alkyl in which the substituent is selected from
- (i) halogen,
- (ii) hydroxy,
- (iii) C₁₋₁₀ alkoxy,
- 20 (iv) C₁₋₅ alkoxycarbonyl,
- (v) C₁₋₅ acyloxy,
- (vi) phenyl,
- (vii) substituted phenyl in which the substituents are X and Y
- (viii) C₁₋₁₀ alkylS(O)_n,
- 25 (ix) C₃₋₈ cycloalkylS(O)_n,
- (x) phenylS(O)_n,
- (xi) substituted phenylS(O)_n in which the substituents are X and Y, and
- (xii) oxo,
- (c) C₁₋₁₀ alkylS(O)_n,
- 30 (d) C₃₋₈ cycloalkylS(O)_n,
- (e) phenylS(O)_n,
- (f) substituted phenylS(O)_n in which the substituents are X and Y,
- (g) halogen,
- (h) hydroxy,
- 35 (i) C₁₋₁₀ alkoxy,
- (j) C₁₋₅ alkoxycarbonyl,
- (k) C₁₋₅ acyloxy,
- (l) phenyl, and
- (m) substituted phenyl in which the substituents are X and Y;
- 40 (7) phenyl;
- (8) substituted phenyl in which the substituents are X and Y;
- (9) amino;
- (10) C₁₋₅ alkylamino;
- (11) di(C₁₋₅ alkyl)amino;
- 45 (12) phenylamino;
- (13) substituted phenylamino in which the substituents are X and Y;
- (14) phenyl C₁₋₁₀ alkylamino;
- (15) substituted phenyl C₁₋₁₀ alkylamino in which the substituents are X and Y;
- (16) a member selected from
- 50 (a) piperidinyl,
- (b) pyrrolidinyl,
- (c) piperazinyl,
- (d) morpholinyl, and
- (e) thiomorpholinyl; and
- 55 (17) R₁₀S in which R₁₀ is selected from
- (a) C₁₋₁₀ alkyl,
- (b) phenyl, and
- (c) substituted phenyl in which the substituents are X and Y;

R₄ is;

- (1) hydrogen;
- (2) C₁₋₁₀ alkyl; and
- (3) substituted C₁₋₁₀ alkyl in which one or more substituents is selected from
 - (a) halogen,
 - (b) hydroxy,
 - (c) C₁₋₁₀ alkoxy
 - (d) C₁₋₅ alkoxycarbonyl,
 - (e) C₁₋₅ alkylacyloxy,
 - (f) phenylacyloxy,
 - (g) phenoxycarbonyl,
 - (h) phenyl C₁₋₅ alkylacyloxy,
 - (i) phenyl C₁₋₅ alkoxy,
 - (j) amino,
 - (k) C₁₋₅ alkylamino,
 - (l) di(C₁₋₅ alkyl)amino,
 - (m) phenylamino,
 - (n) substituted phenylamino in which the substituents are X and Y;
 - (o) phenyl C₁₋₅ alkylamino,
 - (p) substituted phenyl C₁₋₅ alkylamino in which the substituents are X and Y,
 - (q) C₃₋₈ cycloalkyl,
 - (r) phenyl,
 - (s) substituted phenyl in which the substituents are X and Y,
 - (t) phenylS(O)_n,
 - (u) substituted phenyl S(O)_n in which the substituents are X and Y,
 - (v) phenyl C₁₋₅ alkyl S(O)_n,
 - (w) C₁₋₅ alkylS(O)_n;
 - (x) phenylaminoacyloxy,
 - (y) C₁₋₅ alkylaminoacyloxy,
 - (z) C₁₋₅ alkylacylamino,
 - (aa) di(phenylC₁₋₅ alkyl)phosphonyl
 - (bb) di(C₁₋₅ alkyl)phosphinyl
- (4) R₄ together with the carbon atom to which it is attached represents a C₃₋₈ carbocyclic ring;
- R₅ and R₆ independently are H, OH, OR₇ or R₅ and R₆ together with the carbon to which they are attached represent C=O or R₅ and R₆ together with the carbon to which they are attached represent a carbocyclic ring of 3 to 7 atoms; provided that when R₅ is H, R₆ is OH or OR₇, and when R₅ is OH, R₆ is H, and when R₅ is OR₇, R₆ is H;

R₇ is

- $\text{P}(\text{O})\text{R}_8\text{R}_9$, - $\text{C}(\text{O})\text{NR}_8\text{R}_9$, or
- $\text{C}(\text{O})\text{-R}_8$, - $\text{C}(\text{O})\text{-O-R}_8$, phenylC₁₋₃alkyl, C₁₋₅alkyl;
- R₈ and R₉ independently are H, C₁₋₃alkyl, phenylC₁₋₃alkyl or aryl wherein aryl is phenyl naphthyl, pyridyl, furanyl, thienyl or phenyl, naphthyl, pyridyl, furanyl or thienyl substituted with groups X and Y provided that
- when R₇ is
- $\text{C}(\text{O})\text{-O-R}_8$, R₈ is not H and when R₇ is
- $\text{P}(\text{O})\text{-R}_8\text{R}_9$ neither R₈ nor R₉ is H;
- X and Y are independently selected from:
 - a) OH,
 - b) halogen,
 - c) trifluoromethyl,
 - d) C₁₋₃alkoxy,
 - e) C₁₋₃alkylcarbonyloxy,
 - f) phenylcarbonyloxy,
 - g) C₁₋₃alkoxycarbonyl,
 - h) phenyloxy carbonyl,

i) hydrogen;

j) C₁₋₅ alkyl;

Z is selected from

(1) hydrogen;

5 (2) C₁₋₅ alkyl;

(3) substituted C₁₋₅ alkyl in which the substituent is selected from

(a) phenyl,

(b) dimethylamino, and

(c) acetylamino, and

10 (4) 2,3 hydroxypropyl;

halogen is

Cl or F;

a is a single bond or a double bond; provided that when a is a double bond and R₅ or R₆ is OH, the configuration of the 5-position of the naphthyl ring is 5(R); or a pharmaceutically acceptable salt thereof.

15 Except where specifically defined to the contrary, the terms "alkyl", "alkenyl", "acyl", "aryloxy" and "alkoxy" include both the straight-chain and branched chain species of the term.

One embodiment of this invention is the class of compounds of formulae (I) and (II) wherein:

R₁ is selected from:

(1) C₁₋₁₀ alkyl;

20 (2) substituted C₁₋₁₀ alkyl in which one or more substituent(s) is selected from

(a) halogen,

(b) hydroxy,

(c) C₁₋₁₀ alkoxy,

(d) C₁₋₅ alkoxycarbonyl,

25 (e) C₁₋₅ acyloxy,

(f) C₃₋₈ cycloalkyl,

(g) phenyl,

(h) substituted phenyl in which the substituents are X and Y, and

(i) oxo;

30 (3) C₃₋₈ cycloalkyl;

(4) substituted C₃₋₈ cycloalkyl in which one substituent is selected from

(a) C₁₋₁₀ alkyl,

(b) substituted C₁₋₁₀ alkyl in which the substituent is selected from

(i) halogen,

35 (ii) hydroxy,

(iii) C₁₋₁₀ alkoxy

(iv) C₁₋₅ acyloxy,

(v) C₁₋₅ alkoxycarbonyl,

(vi) phenyl,

40 (vii) substituted phenyl in which the substituents are X and Y, and

(viii) oxo,

(c) halogen,

(d) hydroxy,

(e) C₁₋₁₀ alkoxy,

45 (f) C₁₋₅ alkoxycarbonyl,

(g) C₁₋₅ acyloxy,

(h) phenyl,

(i) substituted phenyl in which the substituents are X and Y;

(5) phenylamino;

50 (6) substituted phenylamino in which the substituents are X and Y;

(7) phenylC₁₋₁₀ alkylamino; and

(8) substituted phenyl C₁₋₁₀ alkylamino in which the substituents are X and Y;

R₄ is;

(1) hydrogen;

55 (2) C₁₋₁₀ alkyl;

(3) substituted C₁₋₁₀ alkyl in which one or more substituents is selected from:

(a) halogen,

(b) hydroxy,

- (c) amino;
 (4) CH_2R_{12} in which R_{12} is selected from:
 (a) C_1-5 alkoxy,
 (b) (C_1-5) alkoxy carbonyl,
 5 (c) C_1-5 alkylacyloxy,
 (d) phenylacyloxy,
 (e) phenoxy carbonyl,
 (f) phenyl C_1-5 alkyl,
 (g) phenyl C_1-5 alkoxy
 10 (h) C_1-5 alkylamino,
 (i) di $(\text{C}_1-5$ alkyl)amino,
 (j) phenylamino,
 (k) substituted phenylamino in which the substituents are X and Y,
 (l) phenyl C_1-5 alkylamino,
 15 (m) substituted phenyl C_1-5 alkyl amino in which the substituents are X and Y,
 (n) C_3-8 cycloalkyl,
 (o) phenyl,
 (p) substituted phenyl in which the substituents are X and Y,
 (q) phenyl $\text{S}(\text{O})_n$
 20 (r) substituted phenyl $\text{S}(\text{O})_n$ in which the substituents are X and Y,
 (s) phenyl C_1-5 alkyl $\text{S}(\text{O})_n$,
 (t) C_1-5 alkyl $\text{S}(\text{O})_n$,
 (u) phenylaminoacyloxy,
 (v) C_1-5 alkylaminoacyloxy,
 25 (w) C_1-5 alkylacylamino,
 (x) di(phenyl C_1-5 alkyl)phosphonyl,
 (y) di $(\text{C}_1-5$ alkyl)phosphinyl;
 (5) R_4 together with the carbon atom to which it is attached represents a cyclopropane ring;
 R_5 and R_6 independently are H, OH, OR_7 or R_5 and R_6 together with the carbon to which they are attached
 30 represent $\text{C}=\text{O}$ or R_5 and R_6 together with the carbon to which they are attached represent a cyclopropane
 ring; provided that when R_5 is H, R_6 is OH or OR_7 , and when R_5 is OH, R_6 is H, and when R_5 is OR_7 , R_6 is
 H;
 R_7 is
 35 $-\text{P}(\text{O})-\text{R}_8\text{R}_9$, $-\text{C}(\text{O})-\text{NR}_8\text{R}_9$
 $-\text{C}(\text{O})-\text{R}_8$, $-\text{C}(\text{O})-\text{O}-\text{R}_8$, -phenyl C_1-3 alkyl, C_1-5 alkyl;
 R_8 and R_9 independently are H, C_1-3 alkyl, phenyl C_1-3 alkyl or aryl wherein aryl is phenyl naphthyl, pyridyl,
 furanyl, thienyl or phenyl, naphthyl, pyridyl, furanyl or thienyl substituted with a groups X and Y provided
 40 that when R_7 is
 $-\text{C}(\text{O})-\text{O}-\text{R}_8$, R_8 is not H and when R_7 is
 $-\text{P}(\text{O})-\text{R}_8\text{R}_9$ neither R_8 nor R_9 is H;
 45 X and Y are independently selected from:
 a) OH,
 b) F,
 c) trifluoromethyl,
 d) C_1-3 alkoxy,
 50 e) hydrogen;
 f) C_1-5 alkyl.

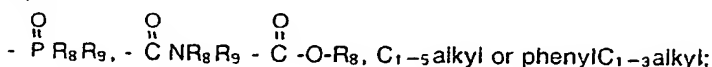
In one subclass are the compounds of formulae (I) and (II) wherein:

R_1 is C_1-10 alkyl; and

R_4 is CH_3 , H, or CH_2 phenyl.

55 Illustrative of this subclass are those compounds of formulae (I) and (II) wherein;

R_7 is



R₈ and R₉ independently are H, C₁₋₃alkyl, phenyl C₁₋₃alkyl or aryl wherein aryl is phenyl or naphthyl or phenyl or naphthyl substituted with X;

Further illustrating this subclass are those compounds wherein:

R₁ is 2-butyl or 2-methyl-2-butyl;

5 R₄ is CH₃.

Exemplifying this subclass are the following compounds:

- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-benzylaminocarbonyloxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 10 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-diphenylphosphinyloxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-(1-phenylethyl-2-oxy)-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 15 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-dibenzylaminocarbonyloxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(S)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(S)-hydroxy-6(S)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 20 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(R)-methyl-1,2,3,4,4a(R),6,7,8,8a(R)-nonahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(S)-methyl-1,2,3,4,4a(R),6,7,8,8a(R)-nonahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 25 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,4a(R),5,6,7,8,8a(R)-octahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one; and the corresponding ring opened dihydroxy acids and esters thereof.

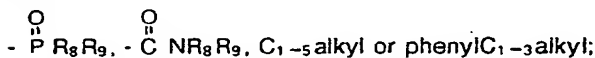
In a second subclass are the compounds of formula (I) and formula (II) wherein:

R₁ is C₁₋₁₀alkyl; and

30 R₄ is CH₂OH, or phenylacyloxymethyl.

Illustrative of this subclass are those compounds of formulae (I) and (II) wherein:

R₇ is



35 R₈ and R₉ independently are H, C₁₋₃alkyl, phenylC₁₋₃alkyl, or aryl wherein aryl is phenyl or naphthyl or phenyl or naphthyl substituted with X;

Further illustrating this subclass are those compounds wherein:

R₁ is 2-butyl or 2-methyl-2-butyl;

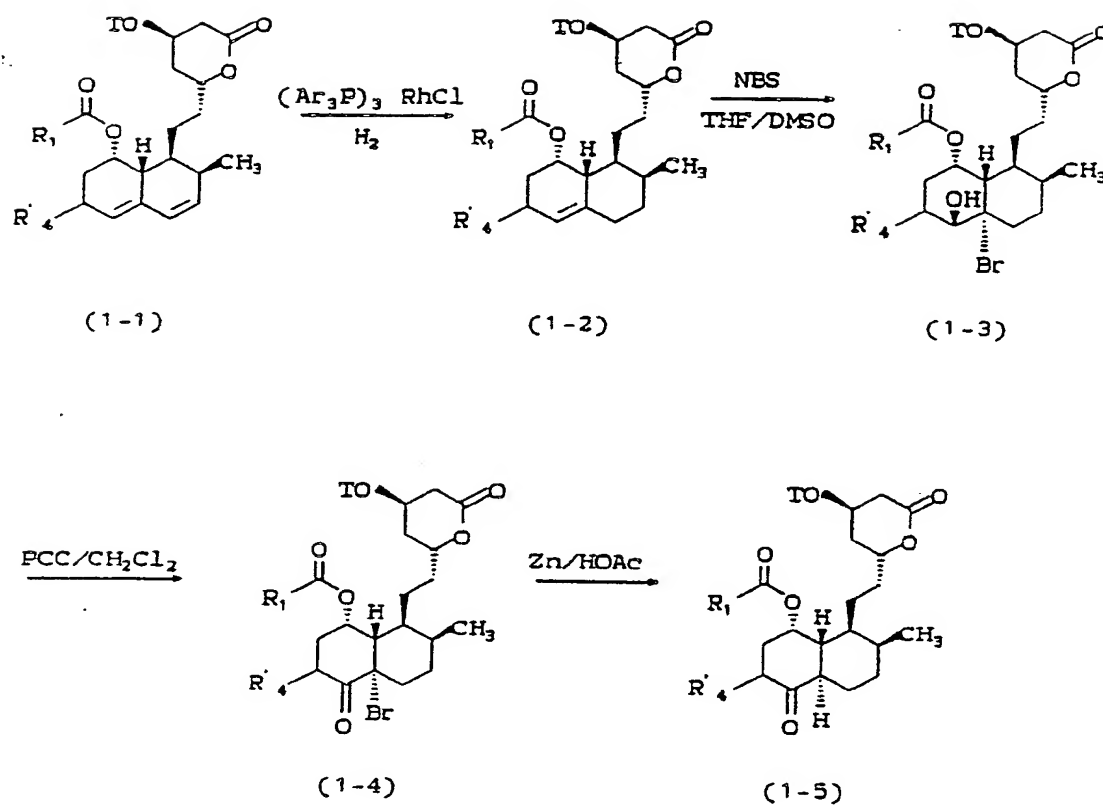
R₄ is CH₂OH.

40 Exemplifying this subclass are the following compounds:

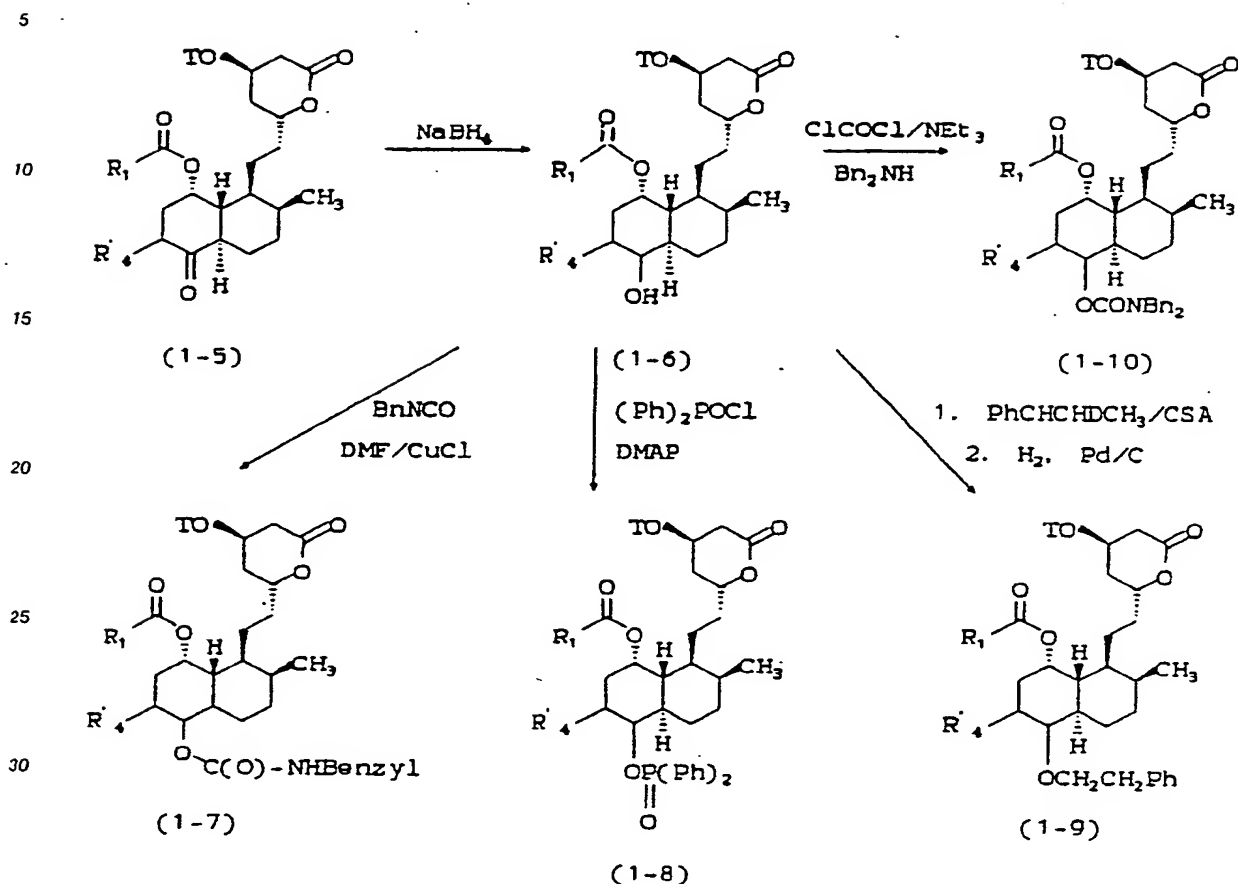
- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-hydroxymethyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-benzylaminocarbonyloxy-6(R)-hydroxymethyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 45 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-diphenylphosphinyloxy-6(R)-hydroxymethyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-(1-phenylethyl-2-oxy)-6(R)-hydroxymethyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-dibenzylaminocarbonyloxy-6(R)-hydroxymethyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 50 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(S)-hydroxymethyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(S)-hydroxy-6(S)-hydroxymethyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one; and the corresponding
- 55 ring opened dihydroxy acids and esters thereof.

The compounds of formula (I) are prepared from lovastatin or mevastatin or a 6-desmethyl-6-hydroxymethyl or 8-acyloxy analog thereof, following the outline in Schemes 1 and 2.

SCHEME 1



SCHEME 1 (continued)



$\text{R}_4 = \text{CH}_3$ or $\text{CH}_2\text{OSi}(\text{Me})_2\text{C}_4\text{H}_9\text{-t}$, or H, T is a hydroxy protecting group such as tert-butyldimethylsilyl, tert-butyldiphenylsilyl, trimethylsilyl, triethylsilyl, triisopropylsilyl or tetrahydropyranyl.

Compound (1-2) is prepared from lovastatin by a reduction of the 3,4 double bond following the procedure detailed in EP 306210 (equivalent to US serial no. 092,804, filed September 3, 1987). The lactone hydroxyl may be protected or unprotected during this reduction. Where R_4 is 6-hydroxymethyl or a protected hydroxymethyl, the conversion of 6-methyl to 6-hydroxymethyl can be accomplished following the procedure in S.N. 254,525, filed October 6, 1988. The hydroxyl group in the lactone ring and at the 6-position of the polyhydronaphthyl ring may be protected (TO) using a silyl protecting group such as tert-butyldimethylsilyl, following the procedure in U.S. Patent 4,444,784. Where the acyl moiety is other than 2-methylbutyryl the acyl group of lovastatin may be hydrolyzed and the hydroxyl group reesterified with an appropriate alkanoyl halide following the procedure in U.S. Patent 4,444,784. The alkanoyl halide can be formed by standard transformations such as substitution with an alkyl moiety or other appropriate electrophile at an acidic C-H site on an available starting material.

The monoene (1-2) is converted to the bromohydrin (1-3) using NBS(N-bromosuccinimide)/THF/DMSO. The bromohydrin (1-3) is oxidized to the intermediate bromoketone (1-4) with pyridinium chlorochromate (PCC) followed by reductive debromination in THF/acetic acid in the presence of zinc to afford ketone (1-5). Reduction of the ketone (1-5) with NaBH_4 in THF/ H_2O gave the epimeric 5-hydroxy derivatives (1-6). This reduction may be carried out on the hydroxyl protected ketone (1-5) or the unprotected ketone where T is H, preferred route is on the protected ketone where T is not H. The benzyl urethane (1-7) is prepared by treating the alcohol (1-6) with benzyl isocyanate in DMF in the presence of CuCl . The alcohol (1-6) can also be treated with β -methoxy styrene in CH_2Cl_2 in the presence of camphorsulfonic acid (CSA) to yield a Z-enol ether which is reduced with H_2 on 10% Pd/C in ethyl acetate to afford the phenethyl ether (1-9). The phosphinate (1-8) is prepared from the alcohol (1-6) by treatment with diphenylphosphinic chloride and 4-

dimethylaminopyridine (DMAP) in CH_2Cl_2 . Dibenzylurethanes (1-10) are formed from the initial treatment of alcohol (1-6) with phosgene followed by reaction with dibenzylamine. The 5-alcohol moiety of compound (1-6) can also be converted to the ester, carbonate and ether functionalities by standard chemical transformations.

5 The 6-hydroxymethyl moiety is converted to a 6-iodomethyl moiety by iodination of the hydroxyl (e.g. iodine, triphenylphosphine, imidazole) followed by substitution or radical mediated coupling with an alkyl or heteroatom moiety which results in the elaboration of CH_2I to R_4 . One example of such methodology is the cross-coupling reaction between an alkyl halide and an organometallic reagent (e.g. alkyl iodides with lithium dialkyl copper-Posner, *Org. React.* 22, 253-400 (1975)).

10 Copending U.S. Patent Application S.N. 254,525 filed October 6, 1988, discloses a method of preparing the 6- α -desmethyl 6- β -methyl lovastatin derivative which can be employed as a starting material in the above scheme. Alternatively removal of the silyl protecting T of the 6- α -methyl ketone (1-5) followed by treatment with 1,8-diazabicyclo [5,4,0] undec-7-ene (DBU) results in the 6- β -methyl ketone (1-5) which after reprotection of the lactone hydroxy group and treatment with NaBH_4 gives a mixture of the 6- β -methyl-5(S)-hydroxy compound (1-6) and the 6- β -methyl-5(R)-hydroxy compound (1-6).

15 The methodology of Scheme 2 may be employed where the compounds of Formula (I) contain a double bond in the 3,4 position.

SCHEME 2

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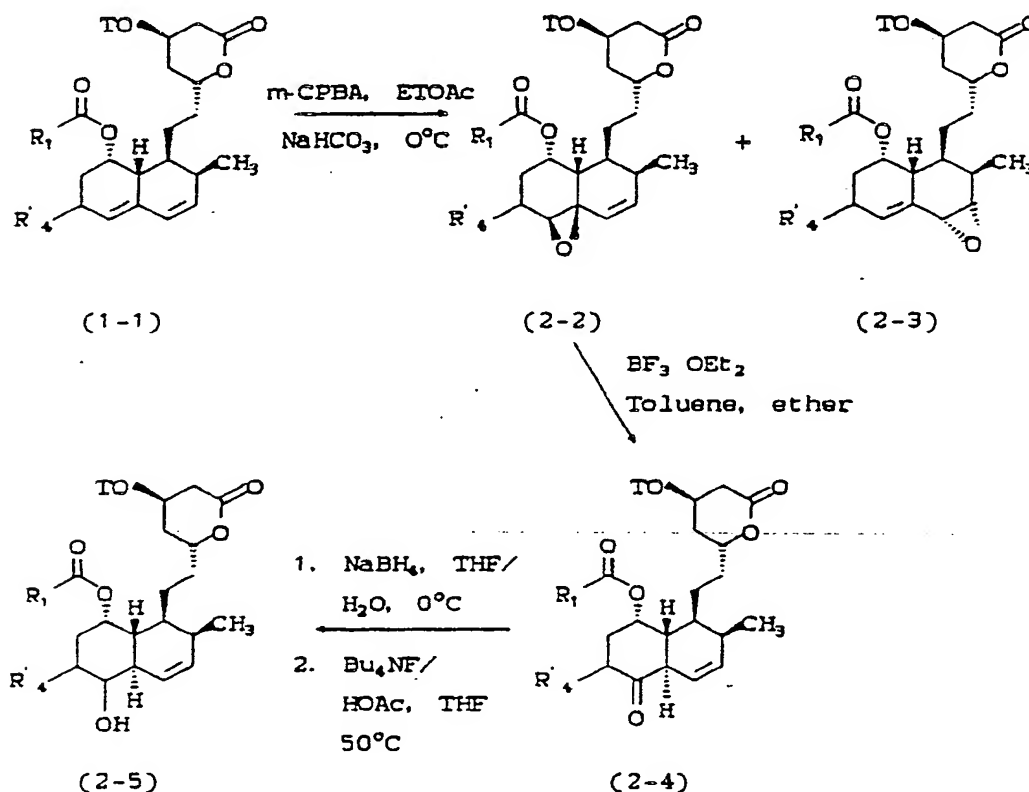
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The hydroxyl protected diene (1-1) is converted to epoxides (2-2) and (2-3) by treatment with m -chloroperoxybenzoic acid at about 0°C . Epoxide (2-2) is then treated with boron trifluoride etherate to form the enone (2-4). The ketone moiety is reduced with NaBH_4 and the lactone hydroxyl deprotected using tetrabutylammonium fluoride to form alcohol (2-5). As described above, the reduction with NaBH_4 may be carried out on the protected or unprotected ($\text{T} = \text{H}$) ketone. The 5-alcohol moiety of compound (2-5) can be further treated to form the OR_7 moieties as described in Scheme 1.

Alternatively the double bond may be inserted following the methodology of Scheme 3.

The bromoketone (1-4), formed as an intermediate in Scheme 1, is isolated and dehydrobrominated with pyridine at about 60 °C to form the eneone (3-2). Thiophenol is added to the olefin of (3-2) to form compound (3-3), which then undergoes oxidative elimination with m-chloroperoxybenzoic acid to form compound (3-4). Ketone (3-4) can be deprotected (3-5) and reduced to alcohol (3-6) which can by standard chemistry be converted to any of the OR₇ moieties described above.

Where the reaction conditions of the above noted chemical transformations would be deleterious to the substituents in the 8-acyloxy moiety, the acetoxy group can be employed as a protecting group which after the elaboration of the 5-position can be removed by hydrolysis to give the 8-hydroxy derivative which then can be acylated according to the general procedures described in U.S. Patent 4,661,483.

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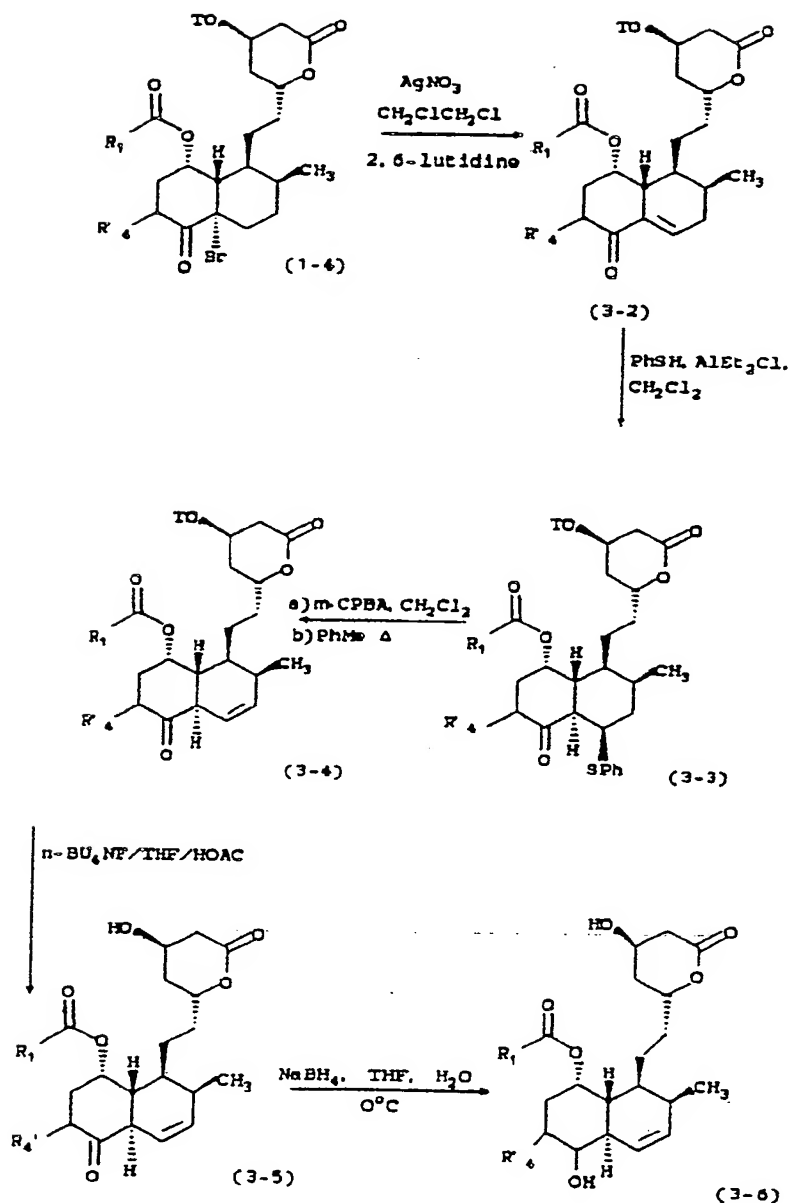
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SCHEME 3



T is a hydroxyl protecting group such as tert-butyldimethylsilyl

Where the product formed by the above described synthetic pathways is not the desired form of that compound, then that product may be subjected to one or more further reactions such as hydrolysis, disilylation, salification, esterification, acylation, ammonolysis or lactonization by conventional methods.

Preferred metal salts are salts with alkali metals, such as sodium or potassium, salts with alkaline earth metals, such as calcium, or salts with other metals such as magnesium, aluminum, iron, zinc, copper, nickel

or cobalt, of which the alkali metal, alkaline earth metal, magnesium and aluminum salts are preferred, the sodium, calcium and aluminum salts being most preferred.

Preferred amino acids to form amino acid salts are basic amino acids, such as arginine, lysine, α,β -diaminobutyric acid or ornithine.

5 Preferred amines to form amine salts include t-octylamine, dibenzylamine, ethylenediamine, morpholine, and tris(hydroxymethyl)aminomethane. Also preferred is ammonia to form the ammonium salt.

Esters are preferably the alkyl esters, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or pentyl esters, of which the methyl ester is preferred. However, other esters such as phenylC₁₋₅alkyl, dimethylamino-C₁₋₅alkyl, or acetylaminoC₁₋₅alkyl may be employed if desired.

10 Metal salts of the carboxylic acids of formula (II) may be obtained by contacting a hydroxide, carbonate or similar solvent with the carboxylic acid of formula (II). The aqueous solvent employed is preferably water, or it may be a mixture of water with an organic solvent, preferably an alcohol (such as methanol or ethanol), a ketone (such as acetone), an aliphatic hydrocarbon (such as hexane) or an ester (such as ethyl acetate). It is preferred to use a mixture of a hydrophilic organic solvent with water. Such reactions are normally
15 conducted at ambient temperature but they may, if desired, be conducted with heating or cooling.

Amine salts of the carboxylic acids of formula (II) may be obtained by contacting an amine in an aqueous solvent with the carboxylic acid of formula (II). Suitable aqueous solvents include water and mixtures of water with alcohols (such as methanol or ethanol), ethers (such as diethyl ether and tetrahydrofuran), nitriles (such as acetonitrile) or ketones (such as acetone); it is preferred to use aqueous
20 acetone as the solvent for this reaction. The reaction is preferably carried out at a temperature of ambient or below, more preferably a temperature of from 5° to 10°C. The reaction immediately goes to completion. Alternatively, a metal salt of the carboxylic acid of formula (II) (which may have been obtained as described above) can be dissolved in an aqueous solvent, after which a mineral acid salt (for example the hydrochloride) of the desired amine is added, employing the same reaction conditions as when the amine
25 itself is reacted with the carboxylic acid of formula (II) and the desired product is then obtained by metathesis.

Amino acid salts of the carboxylic acids of formula (II) may be obtained by contacting an amino acid in aqueous solution with the carboxylic acid of formula (II). Suitable aqueous solvents include water and mixtures of water with alcohols (such as methanol or ethanol) or ethers (such as tetrahydrofuran).

30 Esters, preferably alkyl esters, of the carboxylic acids of formula (II) may be obtained by contacting the carboxylic acid of formula (II) with an appropriate alcohol, preferably in the presence of an acid catalyst, for example a mineral acid (such as hydrochloric acid or sulphuric acid), a Lewis acid (for example boron trifluoride) or an acidic ion exchange resin. The solvent employed for this reaction is not critical, provided that it does not adversely affect the reaction; suitable solvents include the alcohol itself, benzene,
35 chloroform, ethers and the like. Alternatively, the desired product may be obtained by contacting the carboxylic acid of formula (II) with a diazoalkane, in which the alkane moiety may be substituted or unsubstituted. This reaction is usually effected by contacting the acid with an ethereal solution of the diazoalkane. As a further alternative, the ester may be obtained by contacting a metal salt of the carboxylic acid of formula (II) with a halide, preferably an alkyl halide, in a suitable solvent; preferred solvents include
40 dimethylformamide, tetrahydrofuran, dimethylsulfoxide and acetone. Finally, esters may also be obtained from the lactone of formula (I) by reaction with an appropriate alkoxide in an absolute alcohol. All of the reactions for producing esters are preferably effected at about ambient temperature, but, if required by the nature of the reaction system, the reactions may be conducted with heating or cooling.

45 Lactones of the carboxylic acids of formula (I) may be obtained by lactonizing the carboxylic acids of formula (II) under ordinary conditions known to one skilled in the art.

The intrinsic HMG-CoA reductase inhibition activity of the claimed compounds is measured in the in vitro protocol published in J. Med. Chem., 28, p. 347-358 (1985).

For estimation of relative inhibitory potencies, compactin (i.e., mevastatin) was assigned a value of 100 and the IC₅₀ value of the test compound was compared with that of compactin determined simultaneously
50 in the published in vitro protocol.

Representative of the intrinsic HMG-CoA reductase inhibitory activities of the claimed compounds are the following relative potencies for compounds of formula (I):

	<u>Compound</u>	<u>Relative Potency</u>
5	6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-	300
	2(S)-methyl-5(R)-diphenylphosphinyloxy-	
10	6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-	
	decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-	
	3,4,5,6-tetrahydro-2H-pyran-2-one.	
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	<u>Compound</u>	<u>Relative Potency</u>
5	6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-	360
	2(S)-methyl-5(R)-benzylaminocarbonyloxy-	
10	6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-	
	decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-	
	3,4,5,6-tetrahydro-2H-pyran-2-one	
15	6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-	300
	2(S)-methyl-5(R)-(1-phenylethyl-2-oxy)-	
20	6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-	
	decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-	
	3,4,5,6-tetrahydro-2H-pyran-2-one	
25	6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-	94
	2(S)-methyl-5(R)-dibenzylaminocarbonyloxy-	
30	6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-	
	decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-	
	3,4,5,6-tetrahydro-2H-pyran-2-one	
35	6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-	50
	2(S)-methyl-5(R)-hydroxy-6(R)-methyl-	
40	1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydro-	
	naphthyl-1(S)]ethyl]-4(R)-hydroxy-	
	3,4,5,6-tetrahydro-2H-pyran-2-one	
45	6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-	99.6
	2(S)-methyl-5(R)-hydroxy-6(S)-methyl-	
50	1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydro-	
	naphthyl-1(S)]ethyl]-4(R)-hydroxy-	
	3,4,5,6-tetrahydro-2H-pyran-2-one	

	<u>Compound</u>	<u>Relative Potency</u>
5	6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-	11.1
	2(S)-methyl-5(S)-hydroxy-6(S)-methyl-	
10	1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydro-	
	naphthyl-1(S)]ethyl]-4(R)-hydroxy-	
	3,4,5,6-tetrahydro-2H-pyran-2-one	
15	6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-	125
	2(S)-methyl-5-oxo-6(R)-methyl-	
	1,2,3,4,4a(R),6,7,8,8a(R)-nonahydro-	
20	naphthyl-1(S)]ethyl]-4(R)-hydroxy-	
	3,4,5,6-tetrahydro-2H-pyran-2-one	
25	6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-	100
	2(S)-methyl-5-(R)-hydroxy-6(R)-methyl-	
	1,2,4a(R),5,6,7,8,8a(R)-octahydro-	
30	naphthyl-1(S)]ethyl]-4(R)-hydroxy-	
	3,4,5,6-tetrahydro-2H-pyran-2-one.	

The compounds of this invention are useful as antihypercholesterolemic agents for the treatment of arteriosclerosis, hyperlipidemia, familial hypercholesterolemia and like diseases in humans. They may be administered orally or parenterally in the form of a capsule, a tablet, an injectable preparation or the like. It is usually desirable to use the oral route. Doses may be varied, depending on the age, severity, body weight and other conditions of human patients but daily dosage for adults is within the range of from about 10 mg to 2000 mg (preferably 10 to 100 mg) which may be given in two to four divided doses.

The compounds of this invention may also be coadministered with pharmaceutically acceptable nontoxic cationic polymers capable of binding bile acids in a non-reabsorbable form in the gastrointestinal tract. Examples of such polymers include cholestyramine, colestipol and poly[methyl-(3-trimethylaminopropyl)imino-trimethylene dihalide]. The relative amounts of the compounds of this invention and these polymers is between 1:100 and 1:15,000.

Included within the scope of this invention is the method of treating arteriosclerosis, familial hypercholesterolemia or hyperlipidemia which comprises administering to a subject in need of such treatment a nontoxic, therapeutically-effective amount of the compounds of formulae (I) or (II) or pharmaceutical compositions thereof.

Also included within the scope of the present invention is the process for the formation of the 5-hydroxy compound wherein a is a single or a double bond. Further included within the scope of this invention are the intermediate compounds (1-4) and (3-2).

The following examples illustrate the preparation of the compounds of the formulae (I) and (II) and their incorporation into pharmaceutical compositions and as such are not to be considered as limiting the invention set forth in the claims appended hereto:

EXAMPLE 1

Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R)-5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (I-6)

5 Step 1: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-6(R)-methyl-1,2,3,4,6,7,8,8a(S)-octahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (1).

Nitrogen was bubbled through a solution of 50% toluene in absolute ethanol (300 mL) for 5 minutes. Wilkinson's catalyst (5.0 g, 33%/wt.) was added to the solvent and the mixture reduced at room temperature under 50 psi H₂ for 1 hour. Simvastatin (15 g, 36 mmol) was added and the resulting pale yellow solution reduced at room temperature under H₂ (60 psi) for 40 hours. The mixture was concentrated and the residue heated in toluene (700 mL) at 60 °C in the presence of thiourea (5.0 g, 64 mmol) for 1.5 hours. The mixture was cooled to 0 °C (ice bath), filtered, and concentrated. The residue was diluted with 50% EtOAc/hexane and passed through a pad of silica (~250 cc) to give 2 as a beige solid; mp = 128-129 °C (ethyl acetate/hexane); TLC R_f = 0.65 (EtOAc); ¹H NMR (NMR spectra were measured on a Varian XL-300 spectrometer) (CDCl₃) δ 5.36 (bs, 1H), 5.30 (m, 1H), 4.58 (m, 1H), 4.33 (m, 1H), 2.68 (dd, J = 17 and 5 Hz, 1H), 2.68 (m, 1H), 2.59 (dd, J = 17 and 4 Hz, 1H), 2.30-1.20 (m), 1.13 (s, 3H), 1.12 (s, 3H), 1.05 (d, J = 7 Hz, 3H), 0.87 (d, J = 7 Hz, 3H), 0.82 (t, J = 7 Hz, 3H).

20 Step 2: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-6(R)-dimethyl-1,2,3,4,5,7,8,8a(R)-octahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (2)

To a stirred solution of alcohol 1 (5.0 g, 11.9 mmol), imidazole (1.8 g, 26.2 mmol) and dry DMF (30 mL) at 25 °C was added tert-butyldimethylsilyl chloride (2.0 g, 13.0 mmol). After 4 hours the reaction mixture was diluted with petroleum ether, washed with H₂O (2X) and brine, dried (MgSO₄), and concentrated to give the silyl ether 2 as a colorless oil; TLC R_f = 0.70 (50% ether/pet. ether); ¹H NMR (CDCl₃) δ 5.39 (m, 1H), 5.28 (m, 1H), 4.57 (m, 1H), 4.27 (m, 1H), 2.57 (m, 2H), 2.20-1.20 (m), 1.15 (s, 3H), 1.14 (s, 3H), 1.07 (d, J = 7 Hz, 3H), 0.86 (d, J = 7 Hz, 3H), 0.82 (t, J = 7 Hz, 3H).

30 Step 3: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-4a(S)-bromo-5(S)-hydroxy-6(R)-methyl-1,2,3,4,5,6,7,8,8a(R)-nonahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (3)

To a stirred solution of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-6(R)-methyl-1,2,3,4,6,7,8,8a(R)-octahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (95 mg, 0.23 mmol), DMSO (1.0 mL), THF (0.5 mL), and H₂O (12 µL, 0.7 mmol) at 5 °C was added N-bromosuccinimide (NBS) (61 mg, 0.33 mmol). After 1 hour the yellow reaction mixture was diluted with ether, washed with H₂O, saturated NaHCO₃ and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 30% EtOAc/hexane) furnished the bromohydrin as a colorless oil. ¹H NMR (CDCl₃) δ 5.08 (m, 1H), 4.54 (m, 1H), 4.26 (m, 1H), 4.13 (d, J = 3 Hz, 1H), 2.63-2.48 (m, 2H), 2.35-1.1 (m), 1.31 (d, J = 6 Hz, 3H), 1.13 (s, 3H), 1.12 (s, 3H), 0.87 (s, 9H), 0.8 (m, 6H), 0.05 (s, 3H), 0.04 (s, 3H).

45 Step 4: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-4a(S)-bromo-5-oxo-6(R)-methyl-1,2,3,4,6,7,8,8a(R)-octahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (4)

To a stirred mixture of compound 3 (2.4 g, 3.8 mmol), 4A sieves (2.5 g), and dry CH₂Cl₂ (19 ml) at 0 °C was added pyridinium chlorochromate (PCC) (3.2 g, 14.8 mmol). After stirring for 30 minutes, the ice bath was removed with continued stirring for 30 minutes. The reaction mixture was diluted with ether and filtered through a celite pad into a filtration flask containing acetic acid (0.8 mL, 14.0 mmol). Concentration at 10 °C gave the crude bromoketone 4. Flash chromatography (silica, 15% EtOAc/hexanes) gave compound 4 as a solid (m.p. 85-87 °C). ¹H NMR (CDCl₃) δ 5.24 (m, 1H), 4.60 (m, 1H), 4.32 (m, 1H), 2.75 (m, 1H), 2.62 (m, 2H), 2.40-1.20 (m), 1.24 (d, J = 7 Hz, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 0.91 (s, 9H), 0.89 (m, 6H), 0.11 (s, 3H), 0.10 (s, 3H).

Step 5: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(R)-methyl-1,2,3,4,4a(R)-6,7,8,8a(R)-nonahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (5)

- 5 The crude bromoketone 4 (2.6 g, 3.8 mmol) was dissolved in THF/HOAc (38 mL) followed by treatment with zinc (0.74 g, 11.4 mmol) at ambient temperature. After 1.0 hour of vigorous stirring, the reaction mixture was diluted with ether and the excess zinc removed by filtration. The filtrate was washed with H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 15% EtOAc/hexanes) gave compound 5 as a solid (m.p. 147-148 °C).
- 10 ¹H NMR (CDCl₃) δ 5.31(m, 1H), 4.60(m, 1H), 4.29(m, 1H), 2.58(m, 2H), 2.24-1.20(M), 1.24(d, J = 7Hz, 3H), 1.88-(s, 3H), 1.17(s, 3H), 0.89(s, 9H), 0.87(d, J = 7Hz, 3H), 0.83(t, J = 7Hz, 3H), 0.06(s, 6H).

Step 6: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (6)

- To a stirred solution of compound 5 (320 mg, 0.58 mmol), THF (2.6 mL), and H₂O (0.3 mL) at 0 °C was added NaBH₄ (66 mg, 1.7 mmol). After 35 minutes, the reaction mixture was diluted with ethyl acetate, washed with H₂O (2X) and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 20% ethyl acetate/hexane) gave compound 6 as a colorless oil.
- 20 ¹H NMR (CDCl₃) δ 5.06(m, 1H), 4.60(m, 1H), 4.14(m, 1H), 3.45(dd, J = 10 and 5Hz, 1H), 2.56(m, 2H), 2.15-1.15(m), 1.17(s, 3H), 1.16(s, 3H), 1.07(d, J = 7Hz, 3H), 0.88(s, 9H), 0.88(t, J = 7Hz, 3H), 0.86(d, J = 7Hz, 3H), 0.08(s, 3H), 0.08(s, 3H).

Step 7: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R),6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (I-6)

- 30 To a stirred solution of compound 6 (98 mg, 0.18 mmol), THF (530 μL), and HOAc (41 μL, 0.71 mmol) was added tetrabutylammonium fluoride (1M THF, 530 μL, 0.53 mmol) at ambient temperature. After 20 hours, the reaction mixture was diluted with ethyl acetate, washed with H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 60% EtOAc/hexane) gave compound (I-6) as a crystalline solid. mp = 142-143 °C
- 35 ¹H NMR (CDCl₃) δ 5.05(m, 1H), 4.54(m, 1H), 4.31(m, 1H), 3.42(dd, J = 10 and 5Hz, 1H), 2.69(dd, J = 17 and 5Hz, 1H), 2.57(dd, J = 17 and 4Hz, 1H), 2.12-1.10(m), 1.17(s, 3H), 1.16(s, 3H), 1.06(d, J = 7Hz, 3H), 0.82(t, J = 7Hz, 3H), 0.79(d, J = 7Hz, 3H).

Elemental Anal.		
C ₂₅ H ₄₂ O ₅ •0.5H ₂ O:		
Calc'd:	C, 67.08;	H, 9.68
Found:	C, 66.84;	H, 9.31

EXAMPLE 2

Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-benzylaminocarboxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (I-7)

Step 1: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-4a(S)-bromo-5(S)-hydroxy-6(R)-methyl-1,2,3,4,5,6,7,8,8a(R)-nonahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (3)

To a stirred solution of 6(R)-[2-[8(S)-2,2-dimethylbutyryloxy]-2(S)-methyl-6(R)-methyl-1,2,3,4,6,7,8,8a-(R)-octahydronaphthyl-1(S)]ethyl]-4(R)-tert-butylidimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (95 mg, 0.23 mmol) DMSO (1.0 mL), THF (0.5 mL), and H₂O (12 μ L, 0.7 mmol) at 5 °C was added N-bromosuccinimide (NBS) (61 mg, 0.33 mmol). After 1 hour, the yellow reaction mixture was diluted with ether, washed with H₂O, saturated with NaHCO₃, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 30% EtOAc/hexane) furnished the bromohydrin as a colorless oil.
 1H NMR (CDCl₃) δ 5.08(m, 1H), 4.54(m, 1H), 4.26(m, 1H), 4.13(d, J=3 Hz, 1H), 2.63-2.48(m, 2H), 2.35-1.1-(m), 1.31(d, J=6 Hz, 3H), 1.13(s, 3H), 1.12(s, 3H), 0.87(s, 9H), 0.8(m, 6H), 0.05(s, 3H), 0.04(s, 3H).

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Step 2: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(R)-methyl-1,2,3,4,4a(R)-6,7,8,8a(R)-nonahydronaphthyl-1(S)]ethyl]-4(R)-tert-butylidimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (5)

To a stirred mixture of compound 3 (2.4 g, 3.8 mmol), 4A sieves (2.5 g), and dry CH₂Cl₂ (19 ml) at 0 °C was added pyridinium chlorochromate (PCC) (3.2 g, 5.2 mmol). After stirring for 30 minutes, the icebath was removed with continued stirring for 30 minutes. The reaction mixture was diluted with ether and filtered through a celite pad into a filtration flask containing acetic acid (0.8 mL, 14.0 mmol). Concentration at 10 °C gave the crude bromoketone which was reduced immediately. The crude bromoketone was dissolved in THF/HOAc (38 mL) followed by treatment with zinc (0.74 g, 11.4 mmol) at ambient temperature. After 1.0 hour of vigorous stirring, the reaction mixture was diluted with ether and the excess zinc removed by filtration. The filtrate was washed with H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 15% EtOAc/hexanes) gave compound 5 as a solid. (m.p. 147-148 °C)
 1H NMR (CDCl₃) δ 5.31(m, 1H), 4.60(m, 1H), 4.29(m, 1H), 2.58(m, 2H), 2.24-1.20(m), 1.24(d, J=7Hz, 3H), 1.88(s, 3H), 1.17(s, 3H), 0.89(s, 9H), 0.87(d, J=7Hz, 3H), 0.83(t, J=7Hz, 3H), 0.06(s, 6H).

Step 3: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-tert-butylidimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (6)

To a stirred solution of compound 5 (320 mg, 0.58 mmol), THF (2.6 mL), and H₂O (0.3 mL) at 0 °C was added NaBH₄ (66 mg, 1.7 mmol). After 35 minutes, the reaction mixture was diluted with ethyl acetate, washed with H₂O (2X) and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 20% ethyl acetate/hexane) gave compound 6 as a colorless oil.
 1H NMR (CDCl₃) δ 5.06(m, 1H), 4.60(m, 1H), 4.14(m, 1H), 3.45(dd, J=10 and 5Hz, 1H), 2.56(m, 2H), 2.15-1.15(m), 1.17(s, 3H), 1.16(s, 3H), 1.07(d, J=7Hz, 3H), 0.88(s, 9H), 0.88(t, J=7Hz, 3H), 0.86(d, J=7Hz, 3H), 0.08(s, 3H), 0.08(s, 3H).

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Step 4: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-benzylaminocarbonyloxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-tert-butylidimethylsilyloxy-3,4,5,7-tetrahydro-2H-pyran-2-one (7)

To a mixture of compound 6 (227 mg, 0.41 mmol), degassed DMF (2.0 mL), and CuCl (41 mg, 0.41 mmol) at 25 °C was added benzyl isocyanate (82 mg, 0.62 mmol). After 1 hour, the dark green mixture was diluted with ether, washed with H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 20% EtOAc/hexane) furnished compound 7 as a colorless oil.
 1H NMR (CDCl₃) δ 7.30(m, 5H), 5.06(m, 1H), 4.93(m, 1H), 4.61(dd, J=10 and 5Hz, 1H), 4.37(d, J=6Hz, 2H), 4.25(m, 1H), 2.55(m, 2H), 2.27(m, 1H), 2.00-1.10(m), 1.14(s, 3H), 1.13(s, 3H), 0.86(s, 9H), 0.80(m, 9H), 0.06-(s, 6H).

Step 5: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-benzylaminocarbonyloxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (1-7)

Utilizing the same procedure of Example 1, Step 7, the compound 7 (80 mg, 0.11 mmol) was converted

to the desired compound (I-7) which was an amorphous solid.

¹H NMR (CDCl₃) δ 7.30(m, 5H), 5.08(m, 1H), 5.02(t, J=6Hz, 1H), 4.59(dd, J=10 and 5Hz, 1H), 4.54(m, 1H), 4.34(d, J=6Hz, 2H), 4.30(m, 1H), 3.03(bs, 1H), 2.69(dd, J=18 and 5Hz, 1H), 2.58(dd, J=18 and 4Hz, 1H), 2.26(m, 1H), 2.00-1.10(m), 1.14(s, 3H), 1.13(s, 3H), 0.82(t, J=7Hz, 3H), 0.78(d, J=7Hz, 3H).

Elemental Anal. C ₃₃ H ₄₉ O ₇ N•1.5H ₂ O						
Calc'd:	C,	66.20;	H,	8.75	N,	2.34
Found:	C,	65.86;	H,	8.99	N,	2.03

EXAMPLE 3

Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(S)-methyl-1,2,3,4,4a(R)-6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (14)

and

6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(S)-hydroxy-6(S)-methyl-1,2,3,4,4a(R)-6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (15)

Example 1, Steps 1-5 were repeated but substituting tert-butyldiphenylsilyl as the hydroxyl protecting group.

Step 6: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(R)-methyl-1,2,3,4,4a(R)-6,7,8,8a(R)-nonahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (12)

To a stirred solution of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(R)-methyl-1,2,3,4,4a(R)-6,7,8,8a(R)-nonahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (345 mg, 0.63 mmol) and CH₂Cl₂ (3.1 mL) at 0 °C was added HF•pyridine (0.19 g). After 1 hour, the reaction mixture was diluted with ethyl acetate, washed carefully with saturated NaHCO₃ and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 50% ethyl acetate/hexane) furnished compound 12 as a colorless solid.

mp = 159-160 °C

¹H NMR (CDCl₃) δ 5.36(m, 1H), 4.63(m, 1H), 4.40(m, 1H), 2.78(dd, J=18 and 5Hz, 1H), 2.60(m, 2H), 2.20(m, 1H), 2.05-1.15(m), 1.26(d, J=7Hz, 3H), 1.21(s, 3H), 1.20(s, 3H), 0.88(t, J=7Hz, 3H), 0.85(d, J=7Hz, 3H).

Step 7: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(S)-methyl-1,2,3,4,4a(R)-6,7,8,8a(R)-nonahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (13)

A stirred solution of compound 12 (150 mg, 0.34 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (52 μL, 0.34 mmol), and dry toluene was heated at 80 °C for 3 hours. The cooled reaction mixture was concentrated and the residue subjected to flash chromatography (silica, 50% ethyl acetate/hexane) to give the desired compound 13 as a crystalline solid, (m.p. 133-134 °C).

¹H NMR (CDCl₃) δ 5.28(m, 1H), 4.60(m, 1H), 4.48(m, 1H), 2.74(dd, J=18 and 5Hz, 1H), 2.62(m, 2H), 2.47-(ddd, J=9, 9, and 3Hz, 1H), 2.33(m, 1H), 2.00-1.10(m), 1.23(s, 3H), 1.22(s, 3H), 0.98(d, J=7Hz, 3H), 0.87(t, J=7Hz, 3H), 0.80(d, J=7Hz, 3H).

Step 8: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(S)-methyl-1,2,3,4,4a(R)-6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (14)

and

6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(S)-hydroxy-6(S)-methyl-1,2,3,4,4a(R),6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (15)

To a stirred solution of compound 13 (68 mg, 0.15 mmol), THF (1.4 mL), and H₂O (0.15 mL) at 0 °C was added NaBH₄ (11 mg, 0.30 mmol). After 15 minutes, the reaction mixture was diluted with ethyl acetate, washed with H₂O and brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 15% acetone/benzene) gave a faster moving compound 14 and a slower moving compound 15 as amorphous solids.

¹H NMR of compound (14) (CDCl₃) δ 5.08(m, 1H), 4.57(m, 1H), 4.36(m, 1H), 2.86(ddd, J = 10, 5, and 5Hz, 1H), 2.74(dd, J = 18 and 5Hz, 1H), 2.61(m, 1H), 2.05-1.15(m), 1.17(s, 6H), 1.00(d, J = 7Hz, 3H), 0.85(t, J = 7Hz, 3H), 0.83(d, J = 7Hz, 3H).

Elemental Anal. C ₂₅ H ₄₂ O ₆		
Calc'd:	C, 68.46;	H, 9.65
Found:	C, 68.17;	H, 9.50

¹H NMR (CDCl₃) of compound (15) δ 5.14(m, 1H), 4.59(m, 1H), 4.36(m, 1H), 3.53(bs, 1H), 2.74(dd, J = 18 and 5Hz, 1H), 2.60(m, 1H), 2.20(d, J = 3Hz, 1H), 2.00-1.20(m), 1.17(s, 3H), 1.16(s, 3H), 0.95(d, J = 7Hz, 3H), 0.85(t, J = 7Hz, 3H), 0.84(d, J = 7Hz, 3H).

Elemental Anal. C ₂₅ H ₄₂ O ₆		
Calc'd:	C, 68.46;	H, 9.65
Found:	C, 68.09;	H, 9.18

EXAMPLE 4

Preparation of 6(R)-[2-[8(S)-2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-(1-phenylethyl-2-oxy)-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (18)

Example 1, Steps 1-6 were repeated but substituting tert-butyldiphenylsilyl as the hydroxy protecting group.

Step 7: 6(R)-[2-[8(S)-2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-(1-phenylethyl-2-oxy)-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (16)

To a stirred solution of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (270 mg, 0.40 mmol), β-methoxystyrene (165 μL, 1.2 mmol) and dry CH₂Cl₂ (4 mL) at 0 °C was added (±)-camphorsulfonic acid (23 mg, 0.10 mmol). After 15 minutes, the cooling bath was removed and stirring continued for 3 hours. The reaction was quenched with NEt₃ (195 μL, 1.2 mmol) concentrated, and the residue subjected to flash chromatography (silica, 15% EtOAc/hexane) to afford compound 16 as a colorless foam.

¹H NMR (CDCl₃) δ 7.68-7.20(m, 15H), 6.23(d, J = 7Hz, 1H), 5.20(d, J = 7Hz, 1H), 5.09(m, 1H), 4.67(m, 1H), 4.27(m, 1H), 3.56(dd, J = 10 and 5Hz, 1H), 2.57(m, 1H), 2.43(dd, J = 18 and 4Hz, 1H), 2.26(m, 1H), 2.10-1.10(m), 1.17(s, 3H), 1.16(s, 3H), 1.08(s, 9H), 0.86(t, J = 7Hz, 3H), 0.84(d, J = 7Hz, 3H).

Step 8: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-(1-phenylethyl-2-oxy)-6(R)-

methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-tert-butylidiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (17).

A mixture of compound 16 (150 mg, 0.19 mmol) 10% Pd/C (30 mg), and ethyl acetate (5.0 ml) was stirred at 25 °C under a hydrogen atmosphere (1 atm) for 8.0 hours. The reaction mixture was filtered through a celite pad and concentrated. Flash chromatography (silica, 15% ethyl acetate/hexane) gave compound 17 as a colorless oil.

¹H NMR (CDCl₃) δ 7.65-7.20(m, 15H), 5.00(m, 1H), 4.66 (m, 1H), 4.23(m, 1H), 3.78(m, 1H), 3.46(m, 1H), 3.02(dd, J = 10 and 5Hz, 1H), 2.88(ddd, J = 7,7, and 3Hz, 2H), 2.56(m, 1H), 2.41(dd, J = 18 and 4Hz, 1H), 2.22(m, 1H), 2.05-1.10(m), 1.14(s, 3H), 1.08(s, 9H), 0.98(d, J = 7Hz, 3H), 0.82(t, J = 7Hz, 3H), 0.79(d, J = 7Hz, 3H).

Step 9: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-(1-phenylethyl-2-oxy)-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (18)

Utilizing the procedure of Example 1, Step 7 the compound 17 (39 mg, 50 mmol) was converted to the desired compound 18 which was a colorless oil.

¹H NMR (CDCl₃) δ 7.25(m, 5H), 5.05(m, 1H), 4.55(m, 1H), 4.32(m, 1H), 3.73(m, 1H), 3.47 (m, 1H), 3.01(dd, J = 10 and 5Hz, 1H), 2.88 (m, 2H), 2.71(dd, J = 18 and 5Hz, 1H), 2.59 (dd, J = 18 and 4Hz, 1H), 2.22(m, 2H), 2.00-1.10(m), 1.14(s, 3H), 1.13(s, 3H), 0.99 (d, J = 7Hz, 3H), 0.82(t, J = 7Hz, 3H), 0.78(d, J = 7Hz, 3H).

Elemental Analysis: C ₃₃ H ₅₀ O ₆ •0.25 H ₂ O		
Calc'd:	C, 72.43;	H, 9.32
Found:	C, 72.53;	H, 9.32

EXAMPLE 5

Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-dibenzylaminocarbonyloxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (20)

Example 1, Steps 1-6 were repeated but substituting tert-butylidiphenylsilyl as the hydroxy protecting group.

Step 7: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-dibenzylaminocarbonyloxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-tert-butylidiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (19).

A solution of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R)-5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-tert-butylidiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (25 mg, 37 mmol), triethylamine (21 μL, 0.15 mmol), and dry CH₂Cl₂ (200 μL) was added dropwise to a stirred solution of phosgene (20% in toluene, 67 μL, 0.15 mmol) and CH₂Cl₂ (600 μL) at 0 °C. After 5 minutes the cooling bath was removed and the reaction mixture stirred for 20 minutes. Concentration in situ followed by sequential addition of CH₂Cl₂ (400 μL) and dibenzylamine (8 μL, 41 mmol) at ambient temperature, resulted in a heterogeneous mixture. After 15 minutes the reaction mixture was diluted with ether, washed with H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 15-20% ethyl acetate/hexane) gave compound 19 as an oil.

¹H NMR (CDCl₃) δ 7.63-7.26(m, 20H), 5.12(m, 1H), 4.75(dd, J = 10 and 5Hz, 1H), 4.60(m, 1H), 4.40 (m, 2H), 4.33(m, 1H), 2.60(m, 2H), 2.20-1.10(m), 1.17(s, 3H), 1.16(s, 3H), 1.07(s, 9H), 1.00 (d, J = 7Hz, 3H), 0.80(m,

6H).

Step 8: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-dibenzylaminocarbonyloxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (20).

Compound 19 (72 mg, 79 mmol) was dissolved in a premixed solution of tetrabutylammonium fluoride (1M in THF, 300 μ L, 0.3 mmol), HOAc (20 mL, 0.3 mmol), and THF (300 μ L) followed by heating at 50 °C for 1.0 hour. The cooled reaction mixture was diluted with ether, washed with H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 60% EtOAc/hexane) gave compound 20 as a colorless foam.

¹H NMR (CDCl₃) δ 7.37-7.18(m, 10H), 5.11(m, 1H), 4.75(dd, J = 10 and 5Hz, 1H), 4.59(m, 1H), 4.47 (m, 3H), 4.34(m, 1H), 2.72(dd, J = 18 and 5Hz, 1H), 2.61(dd, J = 18 and 3Hz, 1H), 2.32(m, 1H), 2.00-1.10(m), 1.16(s, 3H), 1.15(s, 3H), 1.00(d, J = 7Hz, 3H), 0.84(t, J = 7Hz, 3H), 0.83(d, J = 7Hz, 3H).

Elemental Analysis: C ₄₀ H ₅₅ O ₇ N•0.5 H ₂ O			
Calc'd:	C, 71.61;	H, 8.41;	N, 2.09
Found:	C, 71.66;	H, 8.31;	N, 2.04

EXAMPLE 6

Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-diphenylphosphinyloxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (22)

Example 1, Steps 1-6 were repeated but substituting tert-butyldiphenylsilyl as the hydroxyl protecting group.

Step 7: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-diphenylphosphinyloxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (21).

To a stirred solution of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (59 mg, 87 μ mol) N,N-dimethyl aminopyridine (DMAP) (43 mg, 0.35 mmol), and CH₂Cl₂ (0.44 mL) at ambient temperature was added diphenyl phosphosphinic chloride (33 μ L, 0.17 mmol). After 20 minutes the reaction mixture was diluted with ether, washed with H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 45% EtOAc/hexane) gave compound 21 as an oil.

¹H NMR (CDCl₃) δ 7.85-7.25(m, 20H), 4.98(m, 1H), 4.64(m, 1H), 4.28(m, 2H), 2.55(m, 1H), 2.39(dd, J = 18 and 4Hz, 1H), 2.05-1.10(m), 1.14(s, 3H), 1.13(s, 3H), 1.12(d, J = 7Hz, 3H), 1.03(s, 9H), 0.81(t, J = 7Hz, 3H), 0.73(d, J = 7HZ, 3H).

Step 8: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-diphenylphosphinyloxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (22)

To a stirred solution of compound 21 (64 mg 73 μ mol), THF (0.3 mL), and HOAc (17 μ L, 0.3 mmol) was added tetrabutylammonium fluoride (1M in THF, 300 μ L, 0.3 mmol) followed by heating at 50 °C. After 3.0 hours the cooled reaction mixture was diluted with ether, washed with H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 80% ethyl acetate/hexane) gave compound 22 as a colorless

oil.

¹H NMR (CDCl₃) δ 7.80(m, 4H), 7.46(m, 6H), 5.01(m, 1H), 4.54(m, 1H), 4.30(m, 1H), 4.27(m, 1H), 2.62(m, 3H), 2.10-1.10(m), 1.14(s, 3H), 1.13(s, 3H), 1.12 (d, J = 7Hz, 3H), 0.82(t, J = 7Hz, 3H), 0.73(d, J = 7Hz, 3H).

5

Elemental Analysis:		
C ₃₇ H ₅₁ O ₇ P•0.5 H ₂ O		
Calc'd:	C, 68.60;	H, 8.09
Found:	C, 68.69;	H, 8.03

10

EXAMPLE 7

15

6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,4a(R),5,6,7,8,8a(R)-octahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one; and the corresponding ring opened dihydroxy acids and esters thereof.

20

Step 1: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-6(R)-methyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (23).

25

To a stirred solution of Simvastatin (20.0 g, 48 mmol), imidazole (8.2 g, 0.12 mol), and dry DMF (100 mL) at 25 °C was added tert-butyldiphenylsilylchloride (13.0 mL, 50 mmol). After stirring at 25 °C for 18 hours the reaction mixture was diluted with pet. ether, washed with H₂O (2X) and brine, dried (MgSO₄), and concentrated to furnish (23) as a colorless oil.

30 TLC R_f = 0.75 (silica, 30% ethyl acetate/hexanes); ¹H NMR (CDCl₃) δ 7.63 (m, 4H), 7.42 (m, 6H), 6.00 (d, J = 10 Hz, 1H), 5.80 (dd, J = 10 and 6 Hz, 1H), 5.54 (m, 1H), 5.34 (m, 1H), 4.71 (m, 1H), 4.28 (m, 1H), 2.63-2.23 (m), 2.08-1.20 (m), 1.15 (s, 3H), 1.14 (s, 3H), 1.14 (d, J = 7Hz, 3H), 1.09 (s, 9H), 0.91 (d, J = 7Hz, 3H), 0.84 (t, J = 7Hz, 3H).

35

Step 2: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-4a(R),5(S)-epoxy-6(R)-methyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (24).

40

To a stirred mixture of (23) (47.0 g, 72 mmol), NaHCO₃ (12.0 g, 0.14 mol), and EtOAc (600 mL) at 0 °C was added 55% meta-chloroperbenzoic acid (27.0 g, 86 mmol). After 1.0 h at 0 °C the reaction mixture was diluted with EtOAc, washed sequentially with 10% Na₂SO₃, H₂O, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 10% ethyl acetate/hexanes w/2% triethylamine) gave (24) as an oil. TLC R_f = 0.51 (silica, 30% ethyl acetate/hexanes); ¹H NMR (CDCl₃) δ 7.60 (m, 4H), 7.40 (m, 6H), 6.21 (dd, J = 10 and 6Hz, 1H), 5.12 (d, J = 10 Hz, 1H), 5.11 (m, 1H), 4.68 (m, 1H), 4.24 (m, 1H), 2.96 (s, 1H), 2.60-2.28 (m, 5H), 2.01 (dd, J = 12 and 4Hz, 1H), 1.90-1.20 (m), 1.16 (d, J = 7Hz, 3H), 1.12 (s, 3H), 1.10 (s, 1H) 1.04 (s, 9H), 0.96 (d, J = 7Hz, 3H), 0.80 (t, J = 7Hz, 3H).

45

Step 3: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(R)-methyl-1,2,4a(R)-6,7,8,8a(R)-heptahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (25).

50

A stirred solution of (24) (20.0 g, 30.0 mmol), toluene (150 mL), and ether (150 mL) at -15 °C was treated dropwise with boron trifluoride etherate (3.0 mL, 24.4 mmol) over a 5 minute period. After stirring for 20 minutes the reaction mixture was diluted with ether, washed with sat. NaHCO₃, H₂O, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 12% ethylacetate/hexanes) furnished crude (25) as an oil.

55

TLC R_f = 0.42 (silica, 30% ethyl acetate/hexanes); ¹H NMR (CDCl₃) δ 7.62 (m, 4H) 7.40 (m, 6H), 5.98 (d, J

= 10 Hz, 1H), 5.84 (m, 1H), 5.31 (m, 1H), 4.72 (m, 1H), 4.18 (m, 1H), 3.48 (bd, J = 10 Hz, 1H), 2.63-2.23 (m, 3H), 1.95-1.10 (m), 1.25 (d, J = 7Hz, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.10 (s, 9H), 0.88 (t, J = 7Hz, 3H), 0.85 (d, J = 7Hz, 3H).

5

Step 4: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,4a-(R),5,6,7,8,8a(R)-octahydronaphthyl-1(S)]ethyl]-4(R)-tert-butylidiphenylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (26).

10 To a stirred solution of (25) (6.4 g, 9.5 mmol), THF (90 mL), and H₂O (5 mL) at 0 °C was added 0.36 g (0.95 mmol) NaBH₄ in one portion. After 20 minutes at 0 °C the reaction mixture was diluted with ether, washed with H₂O (2X) and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 20% ethyl acetate/hexanes) gave (26) as a colorless oil.

15 TLC R_f = 0.30 (silica, 35% ethyl acetate/hexanes); ¹H NMR (CDCl₃) δ 7.62 (m, 4H), 7.45 (m, 6H), 5.96 (d, J = 10 Hz, 1H), 5.80 (m, 1H), 5.08 (m, 1H), 4.72 (m, 1H), 4.28 (m, 1H), 3.47 (m, 1H), 2.62-2.10 (m, 5H), 1.85-1.20 (m), 1.16 (s, 3H), 1.15 (s, 3H), 1.10 (d, J = 7Hz, 3H), 1.07 (s, 9H), 0.85 (t, J = 7Hz, 3H), 0.85 (5, J = 7Hz, 3H).

20 Step 5: Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,4a-(R),5,6,7,8,8a(R)-octahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (I-27).

A premixed solution of tetrabutylammonium fluoride (1M in THF, 16 mL, 16.0 mmol) and HOAc (0.92 mL, 16.0 mmol) was added in one portion to a stirred solution of (26) (3.6 g, 5.3 mmol) in THF (32 mL) followed by heating at 50 °C for 3.0 hours. The cooled reaction mixture was diluted with ether, washed with H₂O (2X) and brine, dried (MSO₄), and concentrated. Flash chromatography (silica, 70% ethyl acetate/hexanes) gave (I-27) as a solid. Recrystallization (ethyl acetate/hexanes) gave (I-27) as colorless needles mp = 130-132 °C.

25 TLC R_f = 0.39 (silica, ethyl acetate); ¹H NMR (CDCl₃) δ 5.95 (d, J = 12 Hz, 1H), 5.79 (m, 1H), 5.11 (m, 1H), 4.60 (m, 1H), 4.38 (m, 1H), 3.49 (dt, J = 11 and 6 Hz, 1H), 2.74 (dd, J = 17 and 5Hz, 1H), 2.61 (m, 1H), 2.48 (m, 1H), 2.30 (m, 1H), 2.18 (m, 1H), 2.05-1.20 (m), 1.17 (s, 3H), 1.16 (s, 3H), 1.09 (d, J = 7Hz, 3H), 0.86 (t, J = 8Hz, 3H), 0.85 (d, J = 7Hz, 3H).

35

EXAMPLE 8

40 Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(R)-methyl-1,2,3,6,7,8,8a(R)-heptahydronaphthyl-1(S)]ethyl]-4(R)-tert-butylidimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (11)

A mixture of the bromoketone 4, (50 mg, 79 μmol), from Example 1, step 4, 1,2-dichloroethane (1.0 mL), and 2,6-lutidine (17 μL, 150 mmol) at 25 °C was treated with AgNO₃ (25 mg, 150 mmol). After 2.0 hours the heterogeneous mixture was diluted with ether, washed with H₂O and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, 15% EtOAc/hexanes) gave compound 11 as an oil.

45 ¹H NMR (CDCl₃) δ 6.77 (m, 1H), 5.40 (m, 1H), 4.62 (m, 1H), 4.31 (m, 1H), 2.75-1.10 (m), 1.15 (d, J = 7Hz, 3H), 1.13 (s, 3H), 0.91 (s, 9H), 0.81 (t, J = 7Hz, 3H), 0.79 (d, J = Hz, 3H), 0.10 (s, 6H).

50

EXAMPLES 9-40

Utilizing the general procedures of Examples 1-8, the following compounds of formula (I) are prepared from the appropriately substituted starting materials.

55

<u>Compound No.</u>	<u>R₄</u>	<u>R₅</u>	<u>R₆</u>	<u>a</u>
28	CH ₃	H	O ₂ COCH ₃	-
29	CH ₃	O ₂ COCH ₃	H	-

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	<u>Compound No.</u>	<u>R₄</u>	<u>R₅</u>	<u>R₆</u>	<u>a</u>
	30	CH ₃	H	O ₂ CCH ₃	-
5	31	CH ₃	O ₂ CCH ₃	H	-
	32	H	OH	H	-
	33	H	H	OH	-
	34	CH ₂ OH	OH	H	-
10	35	CH ₂ OH	H	OH	-
	36	CH ₂ Ph	OH	H	-
	37	CH ₂ Ph	H	OH	-
15	38	CH ₂ O ₂ CPh	H	OH	-
	39	CH ₂ O ₂ CPh	OH	H	-
	40	CH ₂ OH	O	O	-
20	41	CH ₂ Ph	O	O	-
	42	H	O	O	-
	43	CH ₂ OH	OCH ₂ Ph	H	-
	44	CH ₂ OH	H	OCH ₂ Ph	-
25	45	CH ₃	OCH ₂ CH ₃	H	-
	46	CH ₃	H	OCH ₂ CH ₃	-
	47	(CH ₂) ₂	OH	H	-
30	48	(CH ₂) ₂	H	OH	-
	49	CH ₃	(CH ₂) ₂		-
	50	CH ₂ OH	OH	H	db
35	51	CH ₂ OH	H	OH	db
	52	H	OH	H	db
	53	H	H	OH	db
	54	CH ₂ Ph	OH	H	db
40	55	CH ₂ Ph	H	OH	db
	56	CH ₃	OCH ₂ CH ₃	H	db
	57	CH ₃	H	OCH ₂ CH ₃	db
45	58	CH ₃	H	O ₂ COCH ₃	db

- = single bond

db = double bond

R₅ = R₆ = O means C=O

EXAMPLE 41

Preparation of Ammonium Salts of Compounds II

The lactone (1.0 mmol) from Example 1 Step 7 is dissolved with stirring in 0.1N NaOH (1.1 mmol) at ambient temperature. The resulting solution is cooled and acidified by the dropwise addition of 1N HCl. The resulting mixture is extracted with diethyl ether and the extract washed with brine and dried (MgSO₄). The MgSO₄ is removed by filtration and the filtrate saturated with ammonia (gas) to give the ammonium salt.

EXAMPLE 42

Preparation of Alkali and Alkaline Earth Salts of Compounds II

To a solution of 44 mg of lactone from Example 1 Step 7 in 2 ml of ethanol is added 1 ml of aqueous 0.1N NaOH. After one hour at room temperature, the mixture is taken to dryness in vacuo to yield the desired sodium salt.

In like manner, the potassium salt is prepared using one equivalent of potassium hydroxide, and the calcium salt, using one equivalent of CaO.

EXAMPLE 43

Preparation of Ethylenediamine Salts of Compounds II

To solution of 0.50 g of the ammonium salt from Example 41 in 10 ml of methanol is added 0.04 ml of ethylenediamine. The methanol is stripped off under vacuum to obtain the desired ethylenediamine salt.

EXAMPLE 44

Preparation of Tris(hydroxymethyl)aminomethane Salts of Compounds II

To a solution of 202 mg of the ammonium salt from Example 41 in 5 ml of methanol is added a solution of 50 mg of tris(hydroxymethyl)aminomethane in 5 ml of methanol. The solvent is removed in vacuo to afford the desired tris(hydroxymethyl)aminomethane salt.

EXAMPLE 45

Preparation of L-Lysine Salts of Compounds II

A solution of 0.001 mole of L-lysine and 0.0011 mole of the ammonium salt from Example 41 in 15 ml of 85% ethanol is concentrated to dryness in vacuo to give the desired L-lysine salt. Similarly prepared are the L-arginine, L-ornithine, and N-methylglucamine salts.

EXAMPLE 46

Preparation of Tetramethylammonium Salts of Compounds II

A mixture of 68 mg of ammonium salt from Example 41 in 2 ml of methylene chloride and 0.08 ml of 24% tetramethylammonium hydroxide in methanol is diluted with ether to yield the desired tetramethylammonium salt.

5

EXAMPLE 4710 Preparation of Methyl Esters of Compounds II

To a solution of 400 mg of lactone from Example 1 Step 7 in 100 ml of absolute methanol is added 10 ml 0.1 M sodium methoxide in absolute methanol. This solution is allowed to stand at room temperature for one hour, then is diluted with water and extracted twice with ethyl acetate. The organic phase is separated,
15 dried (Na_2SO_4), filtered and evaporated in vacuo to yield the desired methyl ester.

In like manner, by the use of equivalent amounts of the alkoxides derived from propanol, butanol, isobutanol, t-butanol, amyl alcohol, isoamyl alcohol, 2-dimethylaminoethanol, benzyl alcohol, phenethanol, 2-acetamidoethanol and the like, and employing the corresponding alcohol, phenethanol, 2-acetamidoethanol and the like, and employing the corresponding alcohol as solvent, the corresponding esters
20 are obtained.

EXAMPLE 48

25

Preparation of Free Dihydroxy Acids

The sodium salt of the compound II from Example 42 is dissolved in 2 ml of ethanol-water (1:1, v:v) and
30 added to 10 ml of 1N hydrochloric acid from which the dihydroxy acid is extracted with ethyl acetate. The organic extract is washed once with water, dried (Na_2SO_4), and evaporated in vacuo with a bath temperature not exceeding 30°C. The dihydroxy acid derivative derived slowly reverts to the corresponding parent lactone on standing at room temperature. The dihydroxy acid form can be maintained by increasing the pH above 7.0.

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EXAMPLE 49

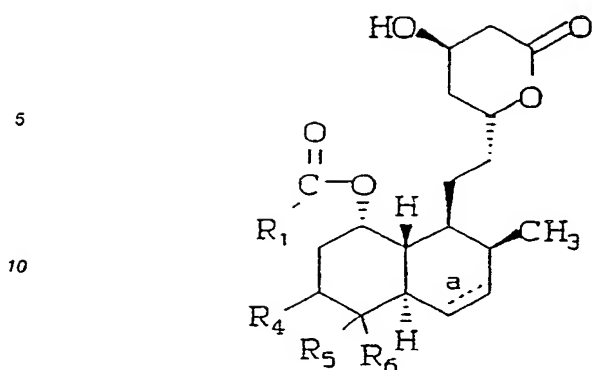
40 As a specific embodiment of a composition of this invention, 20 mg of lactone from Example 1 Step 7 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0, hard-gelatin capsule.

45 Claims

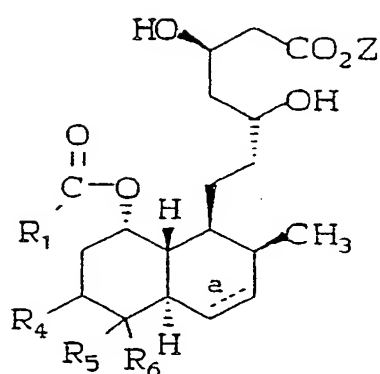
1. A Compound represented by the structural formulae (I) or (II):

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(I)



(II)

20 wherein:

R₁ is selected from:

(1) C₁₋₁₀ alkyl;

(2) substituted C₁₋₁₀ alkyl in which one or more substituent(s) is selected from

(a) halogen,

(b) hydroxy,

(c) C₁₋₁₀ alkoxy,

(d) C₁₋₅ alkoxycarbonyl,

(e) C₁₋₅ acyloxy,

(f) C₃₋₈ cycloalkyl,

(g) phenyl,

(h) substituted phenyl in which the substituents are X and Y,

(i) C₁₋₁₀ alkylS(O)_n in which n is 0 to 2,

(j) C₃₋₈ cycloalkylS(O)_n,

(k) phenylS(O)_n,

(l) substituted phenylS(O)_n in which the substituents are X and Y, and

(m) oxo;

(3) C₁₋₁₀ alkoxy;

(4) C₂₋₁₀ alkenyl;

(5) C₃₋₈ cycloalkyl;

(6) substituted C₃₋₈ cycloalkyl in which one substituent is selected from

(a) C₁₋₁₀ alkyl

(b) substituted C₁₋₁₀ alkyl in which the substituent is selected from

(i) halogen,

(ii) hydroxy,

(iii) C₁₋₁₀ alkoxy,

(iv) C₁₋₅ alkoxycarbonyl,

(v) C₁₋₅ acyloxy,

(vi) phenyl,

(vii) substituted phenyl in which the substituents are X and Y

(viii) C₁₋₁₀ alkylS(O)_n,

(ix) C₃₋₈ cycloalkylS(O)_n,

(x) phenylS(O)_n,

(xi) substituted phenylS(O)_n in which the substituents are X and Y, and

(xii) oxo,

(c) C₁₋₁₀ alkylS(O)_n,

(d) C₃₋₈ cycloalkylS(O)_n,

(e) phenylS(O)_n,

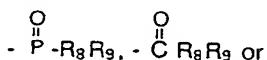
(f) substituted phenylS(O)_n in which the substituents are X and Y,

- (g) halogen,
- (h) hydroxy,
- (i) C₁₋₁₀ alkoxy,
- (j) C₁₋₅ alkoxy carbonyl,
- 5 (k) C₁₋₅ acyloxy,
- (l) phenyl, and
- (m) substituted phenyl in which the substituents are X and Y;
- (7) phenyl;
- (8) substituted phenyl in which the substituents are X and Y;
- 10 (9) amino;
- (10) C₁₋₅ alkylamino;
- (11) di(C₁₋₅ alkyl)amino;
- (12) phenylamino;
- (13) substituted phenylamino in which the substituents are X and Y;
- 15 (14) phenyl C₁₋₁₀ alkylamino;
- (15) substituted phenyl C₁₋₁₀ alkylamino in which the substituents are X and Y;
- (16) a member selected from
 - (a) piperidinyl,
 - (b) pyrrolidinyl,
 - 20 (c) piperazinyl,
 - (d) morpholinyl, and
 - (e) thiomorpholinyl; and
 - (17) R₁₀S in which R₁₀ is selected from
 - (a) C₁₋₁₀ alkyl,
 - 25 (b) phenyl, and
 - (c) substituted phenyl in which the substituents are X and Y;
- R₄ is:
 - (1) halogen;
 - (2) C₁₋₁₀ alkyl; and
 - 30 (3) substituted C₁₋₁₀ alkyl in which one or more substituents is selected from
 - (a) hydrogen,
 - (b) hydroxy,
 - (c) C₁₋₁₀ alkoxy
 - (d) C₁₋₅ alkoxy carbonyl,
 - 35 (e) C₁₋₅ alkylacyloxy,
 - (f) phenylacyloxy,
 - (g) phenoxy carbonyl,
 - (h) phenyl C₁₋₅ alkylacyloxy,
 - (i) phenyl C₁₋₅ alkoxy,
 - 40 (j) amino,
 - (k) C₁₋₅ alkylamino,
 - (l) di(C₁₋₅ alkyl)amino,
 - (m) phenylamino,
 - (n) substituted phenylamino in which the substituents are X and Y;
 - 45 (o) phenyl C₁₋₅ alkylamino,
 - (p) substituted phenyl C₁₋₅ alkylamino in which the substituents are X and Y,
 - (q) C₃₋₈ cycloalkyl,
 - (r) phenyl,
 - (s) substituted phenyl in which the substituents are X and Y,
 - 50 (t) phenylS(O)_n,
 - (u) substituted phenyl S(O)_n in which the substituents are X and Y,
 - (v) phenyl C₁₋₅ alkyl S(O)_n,
 - (w) C₁₋₅ alkylS(O)_n;
 - (x) phenylaminoacyloxy,
 - 55 (y) C₁₋₅ alkylaminoacyloxy,
 - (z) C₁₋₅ alkylacylamino,
 - (aa) di(phenylC₁₋₅ alkyl)phosphonyl
 - (bb) di(C₁₋₅ alkyl)phosphinyl

(4) R_4 together with the carbon atom to which it is attached represents a C_{3-8} carbocyclic ring;
 R_5 and R_6 independently are H, OH, OR₇ or R_5 and R_6 together with the carbon to which they are attached represent C=O or R_5 and R_6 together with the carbon to which they are attached represent a carbocyclic ring of 3 to 7 atoms; provided that when R_5 is H, R_6 is OH or OR₇, and when R_5 is OH, R_6 is H, and when

5 R_5 is OR₇, R_6 is H;

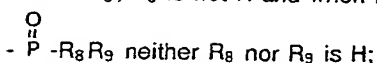
R_7 is



10 $- \overset{\text{O}}{\underset{\text{O}}{\text{C}}} - R_8, - \overset{\text{O}}{\underset{\text{O}}{\text{C}}} - O - R_8, \text{phenylC}_{1-3}\text{alkyl}, \text{C}_{1-5}\text{alkyl};$
 R_8 and R_9 independently are H, C_{1-3} alkyl, phenyl C_{1-3} alkyl or aryl wherein aryl is phenyl, naphthyl, pyridyl, furanyl, thienyl or phenyl, naphthyl, pyridyl, furanyl or thienyl substituted with groups X and Y; provided that

when R_7 is

15 $- \overset{\text{O}}{\underset{\text{O}}{\text{C}}} - O - R_8, R_8$ is not H and when R_7 is



X and Y are independently selected from:

a) OH;

20 b) halogen,

c) trifluoromethyl,

d) C_{1-3} alkoxy,

e) C_{1-3} alkylcarbonyloxy,

f) phenylcarbonyloxy,

25 g) C_{1-3} alkoxycarbonyl,

h) phenyloxycarbonyl,

i) hydrogen,

j) C_{1-5} alkyl;

Z is selected from:

30 (1) hydrogen;

(2) C_{1-5} alkyl;

(3) substituted C_{1-5} in which the substituent is selected from:

(a) phenyl,

(b) dimethylamino, and

35 (c) acetylamino, and

(4) 2,3 dihydroxypropyl;

halogen is Cl or F;

a is a single bond or a double bond; provided that when a is a double bond and R_5 and R_6 is OH, the configuration of the 5-position of the naphthyl ring is 5(R); or a pharmaceutically acceptable salt thereof.

40 2. A Compound of Claim 1 wherein:

R_4 is;

(1) hydrogen;

(2) C_{1-10} alkyl;

(3) substituted C_{1-10} alkyl in which one or more substituents is selected from:

45 (a) halogen,

(b) hydroxy,

(c) amino;

(4) CH_2R_{12} in which R_{12} is selected from:

(a) C_{1-5} alkoxy,

50 (b) C_{1-5} alkoxy carbonyl,

(c) C_{1-5} alkylacyloxy,

(d) phenylacyloxy,

(e) phenoxycarbonyl,

(f) phenyl C_{1-5} alkyl,

55 (g) phenyl C_{1-5} alkoxy

(h) C_{1-5} alkylamino,

(i) di(C_{1-5} alkyl)amino,

(j) phenylamino,

- (k) substituted phenylamino in which the substituents are X and Y,
 (l) phenyl C₁₋₅alkylamino,
 (m) substituted phenylC₁₋₅alkyl amino in which the substituents are X and Y,
 (n) C₃₋₈ cycloalkyl,
 5 (o) phenyl,
 (p) substituted phenyl in which the substituents are X and Y,
 (q) phenylS(O)_n,
 (r) substituted phenyl S(O)_n in which the substituents are X and Y,
 (s) phenyl C₁₋₅ alkyl S(O)_n,
 10 (t) C₁₋₅ alkylS(O)_n,
 (u) phenylaminoacyloxy,
 (v) C₁₋₅ alkylaminoacyloxy,
 (w) C₁₋₅ alkylacylamino,
 (x) di(phenylC₁₋₅alkyl)phosphonyl,
 15 (y) di(C₁₋₅alkyl)phosphinyl;
 (5) R₄ together with the carbon atom to which it is attached represents a cyclopropane ring;
 R₅ and R₆ independently are H, OH, OR₇ or R₅ and R₆ together with the carbon to which they are attached
 represent C=O, or R₅ and R₆ together with the carbon to which they are attached represent a
 cyclopropane ring; provided that when R₅ is H, R₆ is OH or OR₇ and when R₅ is OH, R₆ is H, and when R₅
 20 is OR₇, R₆ is H;
 X and Y are independently selected from:
 a) OH,
 b) F,
 c) trifluoromethyl,
 25 d) C₁₋₃alkoxy,
 e) hydrogen,
 f) C₁₋₅alkyl.

3. A Compound of Claim 2 wherein:

- 30 R₁ is C₁₋₁₀alkyl; and
 R₄ is CH₃, H, or CH₂phenyl;
 R₇ is

$$-\overset{\text{O}}{\underset{\text{O}}{\text{P}}} \text{R}_8 \text{R}_9, -\overset{\text{O}}{\underset{\text{O}}{\text{C}}} \text{NR}_8 \text{R}_9, -\overset{\text{O}}{\underset{\text{O}}{\text{C}}} -\text{O}-\text{R}_8, \text{C}_1-5\text{alkyl or phenylC}_1-3\text{ alkyl};$$

 35 R₈ and R₉ independently are H, C₁₋₃alkyl, phenylC₁₋₃alkyl or aryl wherein aryl is phenyl or naphthyl or
 phenyl or naphthyl substituted with X.

4. A Compound of Claim 3 wherein:

R₁ is 2-butyl or 2-methyl-2-butyl;
 R₄ is CH₃.

- 40 5. A Compound of Claim 2 wherein:

R₁ is C₁₋₁₀alkyl;
 R₄ is CH₂OH or phenylacyloxymethyl;
 R₇ is

- 45
$$-\overset{\text{O}}{\underset{\text{O}}{\text{P}}} \text{R}_8 \text{R}_9, -\overset{\text{O}}{\underset{\text{O}}{\text{C}}} \text{NR}_8 \text{R}_9, \text{ or } \text{C}_1-5\text{alkyl or phenylC}_1-5\text{alkyl};$$

 R₈ and R₉ independently are H, C₁₋₅alkyl, phenylC₁₋₅alkyl or aryl wherein aryl is phenyl or naphthyl or
 phenyl or naphthyl substituted with X.

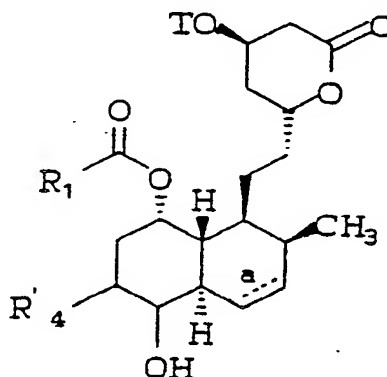
6. A Compound of Claim 5 wherein:

- R₁ is 2-butyl or 2-methyl-2-butyl;
 50 R₄ is CH₂OH.

7. A Compound of Claim 4 selected from:

- 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-
 decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(s)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(S)-hydroxy-6(S)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-
 55 decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-benzylaminocarbonyloxy-6(R)-methyl-1,2,3,4,4a(R)-
 ,5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-diphenylphosphinyloxy-6(R)-methyl-1,2,3,4,4a(R)-

- 5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-(1-phenylethyl-2-oxy)-6(R)-methyl-1,2,3,4,4a(R)-
 5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-dibenzylaminocarbonyloxy-6(R)-methyl-1,2,3,4,4a(R)-
 5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-
 decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,4a(R),5,6,7,8,8a(R)-
 octahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(R)-methyl-1,2,3,4,4a(R),6,7,8,8a(R)-
 nonahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(S)-methyl-1,2,3,4,4a(R),6,7,8,8a(R)-
 nonahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one; and the corresponding ring
 opened dihydroxy acid and esters thereof.
8. A hypocholesterolemic, hypolipidemic pharmaceutical composition comprising a pharmaceutically
 acceptable carrier and a therapeutically effective amount of a compound as defined in Claim 1.
9. A composition of Claim 8 in which the compound is selected from:
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-
 decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(S)-hydroxy-6(S)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-
 decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-benzylaminocarbonyloxy-6(R)-methyl-1,2,3,4,4a(R)-
 5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-diphenylphosphinyloxy-6(R)-methyl-1,2,3,4,4a(R)-
 5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-(1-phenylethyl-2-oxy)-6(R)-methyl-1,2,3,4,4a(R)-
 5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-dibenzylaminocarbonyloxy-6(R)-methyl-1,2,3,4,4a(R)-
 5,6,7,8,8a(R)-decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(R)-methyl-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-
 nonahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5-oxo-6(S)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-
 nonahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(S)-methyl-1,2,4a(R),5,6,7,8,8a(R)-
 decahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S)-methyl-5(R)-hydroxy-6(R)-methyl-1,2,3,4,4a(R),5,6,7,8,8a(R)-
 octahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one; and the corresponding ring
 opened dihydroxy acid and esters.
10. A process for the formation of a compound (1-6):



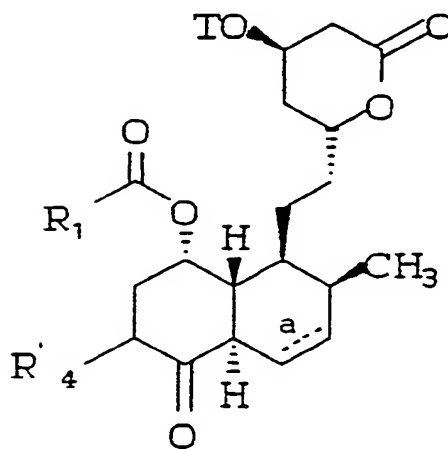
(1-6)

wherein:

R₁ is selected from:

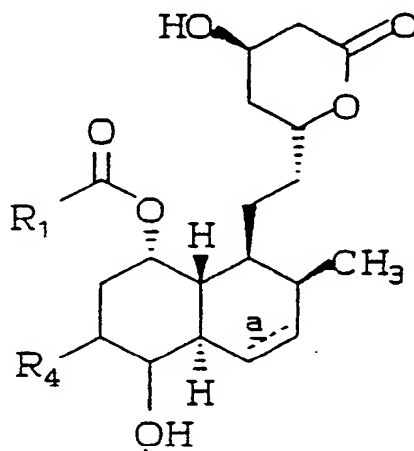
- (1) C₁₋₁₀ alkyl;
- (2) substituted C₁₋₁₀ alkyl in which one or more substituent(s) is selected from
 - 5 (a) halogen,
 - (b) hydroxy,
 - (c) C₁₋₁₀ alkoxy,
 - (d) C₁₋₅ alkoxycarbonyl,
 - (e) C₁₋₅ acyloxy,
 - 10 (f) C₃₋₈ cycloalkyl,
 - (g) phenyl,
 - (h) substituted phenyl in which the substituents are X and Y,
 - (i) C₁₋₁₀ alkylS(O)_n in which n is 0 to 2,
 - (j) C₃₋₈ cycloalkylS(O)_n,
 - 15 (k) phenylS(O)_n,
 - (l) substituted phenylS(O)_n in which the substituents are X and Y, and
 - (m) oxo;
- (3) C₁₋₁₀ alkoxy;
- (4) C₂₋₁₀ alkenyl;
- 20 (5) C₃₋₈ cycloalkyl;
- (6) substituted C₃₋₈ cycloalkyl in which one substituent is selected from
 - (a) C₁₋₁₀ alkyl
 - (b) substituted C₁₋₁₀ alkyl in which the substituent is selected from
 - (i) halogen,
 - 25 (ii) hydroxy,
 - (iii) C₁₋₁₀ alkoxy,
 - (iv) C₁₋₅ alkoxycarbonyl,
 - (v) C₁₋₅ acyloxy,
 - (vi) phenyl,
 - 30 (vii) substituted phenyl in which the substituents are X and Y
 - (viii) C₁₋₁₀ alkylS(O)_n,
 - (ix) C₃₋₈ cycloalkylS(O)_n,
 - (x) phenylS(O)_n,
 - (xi) substituted phenylS(O)_n in which the substituents are X and Y, and
 - 35 (xii) oxo,
 - (c) C₁₋₁₀ alkylS(O)_n,
 - (d) C₃₋₈ cycloalkylS(O)_n,
 - (e) phenylS(O)_n,
 - (f) substituted phenylS(O)_n in which the substituents are X and Y,
 - 40 (g) halogen,
 - (h) hydroxy,
 - (i) C₁₋₁₀ alkoxy,
 - (j) C₁₋₅ alkoxycarbonyl,
 - (k) C₁₋₅ acyloxy,
 - 45 (l) phenyl, and
 - (m) substituted phenyl in which the substituents are X and Y;
 - (7) phenyl;
 - (8) substituted phenyl in which the substituents are X and Y;
 - (9) amino;
 - 50 (10) C₁₋₅ alkylamino;
 - (11) di(C₁₋₅ alkyl)amino;
 - (12) phenylamino;
 - (13) substituted phenylamino in which the substituents are X and Y;
 - (14) phenyl C₁₋₁₀ alkylamino;
 - 55 (15) substituted phenyl C₁₋₁₀ alkylamino in which the substituents are X and Y;
 - (16) a member selected from
 - (a) piperidiny,
 - (b) pyrrolidiny,

- (c) piperazinyl,
 (d) morpholinyl, and
 (e) thiomorpholinyl; and
 (17) $R_{10}S$ in which R_{10} is selected from
- 5 (a) C_{1-10} alkyl,
 (b) phenyl, and
 (c) substituted phenyl in which the substituents are X and Y;
 R_4 is;
 - (1) halogen;
 - 10 (2) C_{1-10} alkyl; and
 (3) substituted C_{1-10} alkyl in which one or more substituents is selected from
 (a) hydrogen,
 (b) OT,
 (c) C_{1-10} alkoxy
 - 15 (d) C_{1-5} alkoxy carbonyl,
 (e) C_{1-5} alkylacyloxy,
 (f) phenylacyloxy,
 (g) phenoxycarbonyl,
 (h) phenyl C_{1-5} alkylacyloxy,
 - 20 (i) phenyl C_{1-5} alkoxy,
 (j) amino,
 (k) C_{1-5} alkylamino,
 (l) di(C_{1-5} alkyl)amino,
 (m) phenylamino,
 - 25 (n) substituted phenylamino in which the substituents are X and Y;
 (o) phenyl C_{1-5} alkylamino,
 (p) substituted phenyl C_{1-5} alkylamino in which the substituents are X and Y,
 (q) C_{3-8} cycloalkyl,
 (r) phenyl,
 - 30 (s) substituted phenyl in which the substituents are X and Y,
 (t) phenyl $S(O)_n$,
 (u) substituted phenyl $S(O)_n$ in which the substituents are X and Y;
 (v) phenyl C_{1-5} alkyl $S(O)_n$,
 (w) C_{1-5} alkyl $S(O)_n$;
 - 35 (x) phenylaminoacyloxy,
 (y) C_{1-5} alkylaminoacyloxy,
 (z) C_{1-5} alkylacylamino,
 (aa) di(phenyl C_{1-5} alkyl)phosphonyl
 (bb) di(C_{1-5} alkyl)phosphinyl
 - 40 (4) R_4 together with the carbon atom to which it is attached represents a C_{3-8} carbocyclic ring;
 X and Y are independently selected from:
 a) OH;
 b) halogen,
 c) trifluoromethyl,
 - 45 d) C_{1-3} alkoxy,
 e) C_{1-3} alkyl carbonyloxy,
 f) phenyl carbonyloxy,
 g) C_{1-3} alkoxy carbonyl,
 h) phenyl oxy carbonyl,
 - 50 i) hydrogen,
 j) C_{1-5} alkyl;
 T is H, tert-butyldimethylsilyl, tert-butyl diphenylsilyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, or
 tetrahydropyranyl;
 halogen is Cl or F;
 - 55 a is a single bond or a double bond; which comprises treatment of a compound



(1-5)

with sodium borohydride to form compound (1-6); and optionally where T is not H, removal of the hydroxyl protecting group by treatment with tetrabutyl ammonium fluoride and acetic acid to form a compound (1-6)



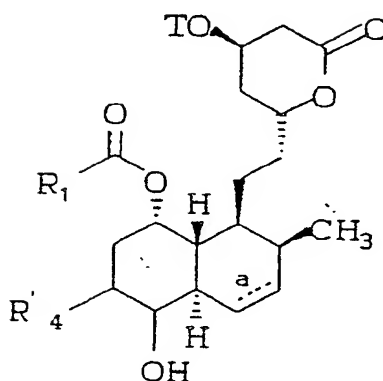
(1-6)

wherein :

R₄ is R₄' where T is H.

Claims for the following Contracting State: GR

1. A process for the formation of a compound (1-6):



(1-6)

wherein:

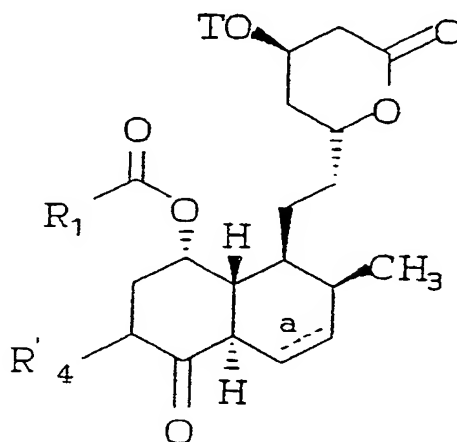
R_1 is selected from:

- (1) C_{1-10} alkyl;
- (2) substituted C_{1-10} alkyl in which one or more substituent(s) is selected from
 - (a) halogen,
 - (b) hydroxy,
 - (c) C_{1-10} alkoxy,
 - (d) C_{1-5} alkoxycarbonyl,
 - (e) C_{1-5} acyloxy,
 - (f) C_{3-8} cycloalkyl,
 - (g) phenyl,
 - (h) substituted phenyl in which the substituents are X and Y,
 - (i) C_{1-10} alkylS(O) $_n$ in which n is 0 to 2,
 - (j) C_{3-8} cycloalkylS(O) $_n$,
 - (k) phenylS(O) $_n$,
 - (l) substituted phenylS(O) $_n$ in which the substituents are X and Y, and
 - (m) oxo;
- (3) C_{1-10} alkoxy;
- (4) C_{2-10} alkenyl;
- (5) C_{3-8} cycloalkyl;
- (6) substituted C_{3-8} cycloalkyl in which one substituent is selected from
 - (a) C_{1-10} alkyl
 - (b) substituted C_{1-10} alkyl in which the substituent is selected from
 - (i) halogen,
 - (ii) hydroxy,
 - (iii) C_{1-10} alkoxy,
 - (iv) C_{1-5} alkoxycarbonyl,
 - (v) C_{1-5} acyloxy,
 - (vi) phenyl,
 - (vii) substituted phenyl in which the substituents are X and Y
 - (viii) C_{1-10} alkylS(O) $_n$,
 - (ix) C_{3-8} cycloalkylS(O) $_n$,
 - (x) phenylS(O) $_n$,
 - (xi) substituted phenylS(O) $_n$ in which the substituents are X and Y, and
 - (xii) oxo,
- (c) C_{1-10} alkylS(O) $_n$,
- (d) C_{3-8} cycloalkylS(O) $_n$,
- (e) phenylS(O) $_n$,
- (f) substituted phenylS(O) $_n$ in which the substituents are X and Y,

- (g) halogen,
- (h) hydroxy,
- (i) C₁₋₁₀ alkoxy,
- (j) C₁₋₅ alkoxy carbonyl,
- 5 (k) C₁₋₅ acyloxy,
- (l) phenyl, and
- (m) substituted phenyl in which the substituents are X and Y;
- (7) phenyl;
- (8) substituted phenyl in which the substituents are X and Y;
- 10 (9) amino;
- (10) C₁₋₅ alkylamino;
- (11) di(C₁₋₅ alkyl)amino;
- (12) phenylamino;
- (13) substituted phenylamino in which the substituents are X and Y;
- 15 (14) phenyl C₁₋₁₀ alkylamino;
- (15) substituted phenyl C₁₋₁₀ alkylamino in which the substituents are X and Y;
- (16) a member selected from
- (a) piperidinyl,
- (b) pyrrolidinyl,
- 20 (c) piperazinyl,
- (d) morpholinyl, and
- (e) thiomorpholinyl; and
- (17) R₁₀S in which R₁₀ is selected from
- (a) C₁₋₁₀ alkyl,
- 25 (b) phenyl, and
- (c) substituted phenyl in which the substituents are X and Y;
- R₄ is;
- (1) halogen;
- (2) C₁₋₁₀ alkyl; and
- 30 (3) substituted C₁₋₁₀ alkyl in which one or more substituents is selected from
- (a) hydrogen,
- (b) OT,
- (c) C₁₋₁₀ alkoxy
- (d) C₁₋₅ alkoxy carbonyl,
- 35 (e) C₁₋₅ alkylacyloxy,
- (f) phenylacyloxy,
- (g) phenoxy carbonyl,
- (h) phenyl C₁₋₅ alkylacyloxy,
- (i) phenyl C₁₋₅ alkoxy,
- 40 (j) amino,
- (k) C₁₋₅ alkylamino,
- (l) di(C₁₋₅ alkyl)amino,
- (m) phenylamino,
- (n) substituted phenylamino in which the substituents are X and Y;
- 45 (o) phenyl C₁₋₅ alkylamino,
- (p) substituted phenyl C₁₋₅ alkylamino in which the substituents are X and Y,
- (q) C₃₋₈ cycloalkyl,
- (r) phenyl,
- (s) substituted phenyl in which the substituents are X and Y,
- 50 (t) phenylS(O)_n,
- (u) substituted phenyl S(O)_n in which the substituents are X and Y,
- (v) phenyl C₁₋₅ alkyl S(O)_n,
- (w) C₁₋₅ alkylS(O)_n;
- (x) phenylaminoacyloxy,
- 55 (y) C₁₋₅ alkylaminoacyloxy,
- (z) C₁₋₅ alkylacylamino,
- (aa) di(phenylC₁₋₅ alkyl)phosphonyl
- (bb) di(C₁₋₅ alkyl)phosphinyl

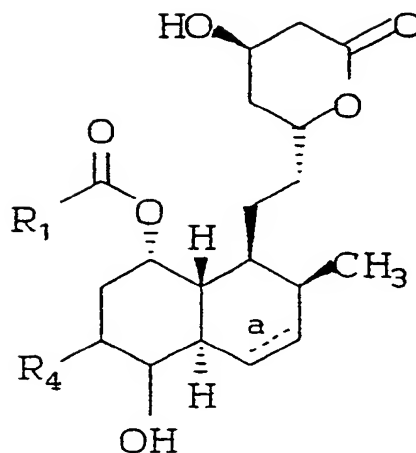
(4) R'_4 together with the carbon atom to which it is attached represents a C_3-8 carbocyclic ring;
X and Y are independently selected from:

- a) OH;
 - b) halogen,
 - 5 c) trifluoromethyl,
 - d) C_1-3 alkoxy,
 - e) C_1-3 alkylcarbonyloxy,
 - f) phenylcarbonyloxy,
 - g) C_1-3 alkoxycarbonyl,
 - 10 h) phenyloxycarbonyl,
 - i) hydrogen,
 - j) C_1-5 alkyl;
- T is H, tert-butyldimethylsilyl, tert-butyl diphenylsilyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, or tetrahydropyranyl;
- 15 halogen is Cl or F;
- a is a single bond or a double bond; which comprises treatment of a compound



(1-5)

with sodium borohydride to form compound (1-6); and optionally where T is not H, removal of the hydroxyl
40 protecting group by treatment with tetrabutyl ammonium fluoride and acetic acid to form a compound



(1-6)

Wherein R_4 is R'_4 where T is H.

2. A process according to Claim 1 wherein:

R'_4 is:

- (1) hydrogen;
 - (2) C_{1-10} alkyl;
 - (3) substituted C_{1-10} alkyl in which one or more substituents is selected from:
 - (a) halogen,
 - (b) OT,
 - (c) amino;
 - (4) CH_2R_{12} in which R_{12} is selected from:
 - (a) C_{1-5} alkoxy,
 - (b) C_{1-5} alkoxy carbonyl,
 - (c) C_{1-5} alkylacyloxy,
 - (d) phenylacyloxy,
 - (e) phenoxycarbonyl,
 - (f) phenyl C_{1-5} alkyl,
 - (g) phenyl C_{1-5} alkoxy
 - (h) C_{1-5} alkylamino,
 - (i) di(C_{1-5} alkyl)amino,
 - (j) phenylamino,
 - (k) substituted phenylamino in which the substituents are X and Y,
 - (l) phenyl C_{1-5} alkylamino,
 - (m) substituted phenyl C_{1-5} alkyl amino in which the substituents are X and Y,
 - (n) C_{3-8} cycloalkyl,
 - (o) phenyl,
 - (p) substituted phenyl in which the substituents are X and Y,
 - (q) phenylS(O) $_n$
 - (r) substituted phenyl S(O) $_n$ in which the substituents are X and Y,
 - (s) phenyl C_{1-5} alkylS(O) $_n$,
 - (t) C_{1-5} alkylS(O) $_n$,
 - (u) phenylaminoacyloxy,
 - (v) C_{1-5} alkylaminoacyloxy,
 - (w) C_{1-5} alkylacylamino,
 - (x) di(phenyl C_{1-5} alkyl)phosphonyl,
 - (y) di(C_{1-5} alkyl)phosphinyl;
 - (5) R'_4 together with the carbon atom to which it is attached represents a cyclopropane ring;
- X and Y are independently selected from:

- a) OH;
 b) F,
 c) trifluoromethyl,
 d) C₁₋₃alkoxy,
 e) hydrogen,
 f) C₁₋₅alkyl.

3. A process according to Claim 2 wherein:

R₁ is C₁₋₁₀alkyl; and

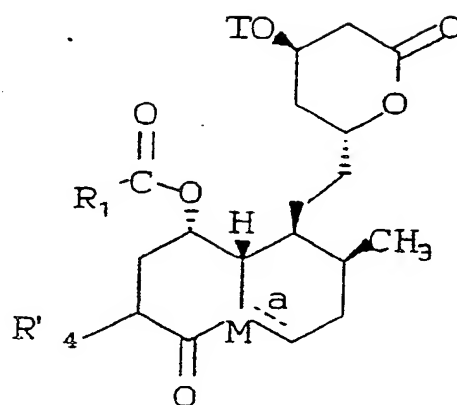
R₄ is CH₃, H, CH₂phenyl, or CH₂OT.

4. A process according to Claim 3 wherein:

R₁ is 2-butyl or 2-methyl-2-butyl;

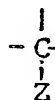
R₄ is CH₃.

5. A compound of structural formula:



wherein:

M is



- C = C;

Z is Cl or Br;

T is H, tert-butyldimethylsilyl, tert-butyl diphenylsilyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, or tetrahydropyranyl;

R₁ is selected from:

(1) C₁₋₁₀ alkyl;

(2) substituted C₁₋₁₀ alkyl in which one or more substituent(s) is selected from
 (a) halogen,

(b) hydroxy,

(c) C₁₋₁₀ alkoxy,

(d) C₁₋₅ alkoxycarbonyl,

(e) C₁₋₅ acyloxy,

(f) C₃₋₈ cycloalkyl,

(g) phenyl,

(h) substituted phenyl in which the substituents are X and Y,

(i) C₁₋₁₀ alkylS(O)_n in which n is 0 to 2,

(j) C₃₋₈ cycloalkylS(O)_n.

- (k) phenylS(O)_n,
 - (l) substituted phenylS(O)_n in which the substituents are X and Y, and
 - (m) oxo;
 - (3) C₁₋₁₀ alkoxy;
 - 5 (4) C₂₋₁₀ alkenyl;
 - (5) C₃₋₈ cycloalkyl;
 - (6) substituted C₃₋₈ cycloalkyl in which one substituent is selected from
 - (a) C₁₋₁₀ alkyl
 - (b) substituted C₁₋₁₀ alkyl in which the substituent is selected from
 - 10 (i) halogen,
 - (ii) hydroxy,
 - (iii) C₁₋₁₀ alkoxy,
 - (iv) C₁₋₅ alkoxycarbonyl,
 - (v) C₁₋₅ acyloxy,
 - 15 (vi) phenyl,
 - (vii) substituted phenyl in which the substituents are X and Y
 - (viii) C₁₋₁₀ alkylS(O)_n,
 - (ix) C₃₋₈ cycloalkylS(O)_n,
 - (x) phenylS(O)_n.
 - 20 (xi) substituted phenylS(O)_n in which the substituents are X and Y, and
 - (xii) oxo,
 - (c) C₁₋₁₀ alkylS(O)_n,
 - (d) C₃₋₈ cycloalkylS(O)_n,
 - (e) phenylS(O)_n.
 - 25 (f) substituted phenylS(O)_n in which the substituents are X and Y,
 - (g) halogen,
 - (h) hydroxy,
 - (i) C₁₋₁₀ alkoxy,
 - (j) C₁₋₅ alkoxycarbonyl,
 - 30 (k) C₁₋₅ acyloxy,
 - (l) phenyl, and
 - (m) substituted phenyl in which the substituents are X and Y;
 - (7) phenyl;
 - (8) substituted phenyl in which the substituents are X and Y;
 - 35 (9) amino;
 - (10) C₁₋₅ alkylamino;
 - (11) di(C₁₋₅ alkyl)amino;
 - (12) phenylamino;
 - (13) substituted phenylamino in which the substituents are X and Y;
 - 40 (14) phenyl C₁₋₁₀ alkylamino;
 - (15) substituted phenyl C₁₋₁₀ alkylamino in which the substituents are X and Y;
 - (16) a member selected from
 - (a) piperidinyl,
 - (b) pyrrolidinyl,
 - 45 (c) piperazinyl,
 - (d) morpholinyl, and
 - (e) thiomorpholinyl; and
 - (17) R₅S in which R₅ is selected from
 - (a) C₁₋₁₀ alkyl.
 - 50 (b) phenyl, and
 - (c) substituted phenyl in which the substituents are X and Y;
- R₄ is CH₃, CH₂OT or H;
 X and Y are independently selected from:
- a) OH,
 - 55 b) halogen,
 - c) trifluoromethyl,
 - d) C₁₋₃alkoxy,
 - e) C₁₋₃alkylcarbonyloxy,

- f) phenylcarbonyloxy,
- g) C₁₋₃alkoxycarbonyl,
- h) phenyloxy carbonyl,
- i) hydrogen;

5 j) C₁₋₅alkyl;

a is a single bond or a double bond provided that when M is C-Z, a is a single bond.

6. A compound according to Claim 5 wherein:

M is

10 $-\overset{\overset{|}{\text{C}}}{\text{C}}-\text{Z};$

Z is Br;

R₁ is selected from:

(1) C₁₋₁₀ alkyl;

(2) substituted C₁₋₁₀ alkyl in which one or more substituent(s) is selected from

15 (a) halogen,

(b) hydroxy,

(c) C₁₋₁₀ alkoxy,

(d) C₁₋₅ alkoxycarbonyl,

(e) C₁₋₅ acyloxy,

20 (f) C₃₋₈ cycloalkyl,

(g) phenyl,

(h) substituted phenyl in which the substituents are X and Y, and

(i) oxo;

(3) C₃₋₈ cycloalkyl;

25 (4) substituted C₃₋₈ cycloalkyl in which one substituent is selected from

(a) C₁₋₁₀ alkyl,

(b) substituted C₁₋₁₀ alkyl in which the substituent is selected from

(i) halogen,

(ii) hydroxy,

30 (iii) C₁₋₁₀ alkoxy,

(iv) C₁₋₅ acyloxy,

(v) C₁₋₅ alkoxycarbonyl,

(vi) phenyl,

(vii) substituted phenyl in which the substituents are X and Y, and

35 (viii) oxo,

(c) halogen,

(d) hydroxy,

(e) C₁₋₁₀ alkoxy,

(f) C₁₋₅ alkoxycarbonyl,

40 (g) C₁₋₅ acyloxy,

(h) phenyl,

(i) substituted phenyl in which the substituents are X and Y;

(5) phenylamino;

(6) substituted phenylamino in which the substituents are X and Y;

45 (7) phenylC₁₋₁₀alkylamino and;

(8) substituted phenyl C₁₋₁₀ alkylamino in which the substituents are X and Y;
X and Y are independently selected from

a) OH,

b) F,

50 c) trifluoromethyl,

d) C₁₋₃alkoxy,

e) hydrogen;

f) C₁₋₅alkyl.

7. A compound according to Claim 6 wherein:

55 R₁ is C₁₋₁₀alkyl;

R₄ is CH₃.

8. A compound according to Claim 7 selected from the group wherein;

(a) R₁ is 2-methyl-2-butyl;

T is *tert*-butyldimethylsilyl;

M is $\overline{\text{C}}\text{-Z}$;

Z is Br;

(b) R₁ is 2-butyl;

5 T is *tert*-butyldimethylsilyl;

M is $\overline{\text{C}}\text{-Z}$;

Z is Br;

(c) R₁-2-methyl-2-butyl,

T is *tert*-butyldimethylsilyl.

10 M is $\overline{\text{C}}=\text{C}$, a is a double bond;

(d) R₁ is 2-butyl,

T is *tert*-butyldimethylsilyl,

M is $\overline{\text{C}}=\text{C}$, a is a double bond.

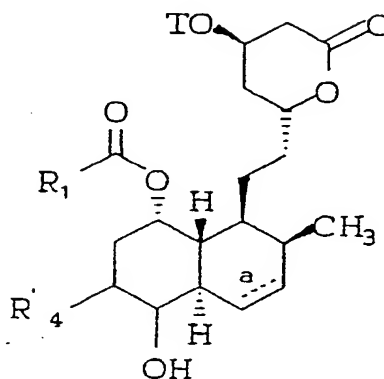
15 Claims for the following Contracting State: ES

1. A process for the formation of a compound (1-6):

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25

30



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(1-6)

wherein:

R₁ is selected from:

40 (1) C₁₋₁₀ alkyl;

(2) substituted C₁₋₁₀ alkyl in which one or more substituent(s) is selected from

(a) halogen,

(b) hydroxy,

(c) C₁₋₁₀ alkoxy,

45 (d) C₁₋₅ alkoxy carbonyl,

(e) C₁₋₅ acyloxy,

(f) C₃₋₈ cycloalkyl,

(g) phenyl,

(h) substituted phenyl in which the substituents are X and Y,

50 (i) C₁₋₁₀ alkylS(O)_n in which n is 0 to 2,

(j) C₃₋₈ cycloalkylS(O)_n,

(k) phenylS(O)_n,

(l) substituted phenylS(O)_n in which the substituents are X and Y, and

(m) oxo;

55 (3) C₁₋₁₀ alkoxy;

(4) C₂₋₁₀ alkenyl;

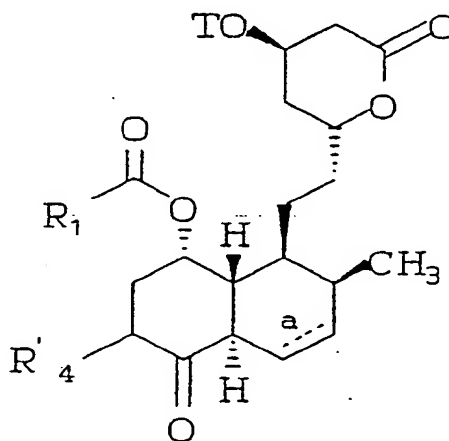
(5) C₃₋₈ cycloalkyl;

(6) substituted C₃₋₈ cycloalkyl in which one substituent is selected from

(a) C₁₋₁₀ alkyl

- (b) substituted C_{1-10} alkyl in which the substituent is selected from
- (i) halogen,
 - (ii) hydroxy,
 - (iii) C_{1-10} alkoxy,
 - 5 (iv) C_{1-5} alkoxycarbonyl,
 - (v) C_{1-5} acyloxy,
 - (vi) phenyl,
 - (vii) substituted phenyl in which the substituents are X and Y
 - (viii) C_{1-10} alkylS(O)_n,
 - 10 (ix) C_{3-8} cycloalkylS(O)_n,
 - (x) phenylS(O)_n,
 - (xi) substituted phenylS(O)_n in which the substituents are X and Y, and
 - (xii) oxo,
 - (c) C_{1-10} alkylS(O)_n,
 - 15 (d) C_{3-8} cycloalkylS(O)_n,
 - (e) phenylS(O)_n,
 - (f) substituted phenylS(O)_n in which the substituents are X and Y,
 - (g) halogen,
 - (h) hydroxy,
 - 20 (i) C_{1-10} alkoxy,
 - (j) C_{1-5} alkoxycarbonyl,
 - (k) C_{1-5} acyloxy,
 - (l) phenyl, and
 - (m) substituted phenyl in which the substituents are X and Y;
 - 25 (7) phenyl;
 - (8) substituted phenyl in which the substituents are X and Y;
 - (9) amino;
 - (10) C_{1-5} alkylamino;
 - (11) di(C_{1-5} alkyl)amino;
 - 30 (12) phenylamino;
 - (13) substituted phenylamino in which the substituents are X and Y;
 - (14) phenyl C_{1-10} alkylamino;
 - (15) substituted phenyl C_{1-10} alkylamino in which the substituents are X and Y;
 - (16) a member selected from
 - 35 (a) piperidinyl,
 - (b) pyrrolidinyl,
 - (c) piperazinyl,
 - (d) morpholinyl, and
 - (e) thiomorpholinyl; and
 - 40 (17) $R_{10}S$ in which R_{10} is selected from
 - (a) C_{1-10} alkyl,
 - (b) phenyl, and
 - (c) substituted phenyl in which the substituents are X and Y;
 - R_4 is;
 - 45 (1) halogen;
 - (2) C_{1-10} alkyl; and
 - (3) substituted C_{1-10} alkyl in which one or more substituents is selected from
 - (a) hydrogen,
 - (b) OT,
 - 50 (c) C_{1-10} alkoxy
 - (d) C_{1-5} alkoxycarbonyl,
 - (e) C_{1-5} alkylacyloxy,
 - (f) phenylacyloxy,
 - (g) phenoxycarbonyl,
 - 55 (h) phenyl C_{1-5} alkylacyloxy,
 - (i) phenyl C_{1-5} alkoxy,
 - (j) amino,
 - (k) C_{1-5} alkylamino,

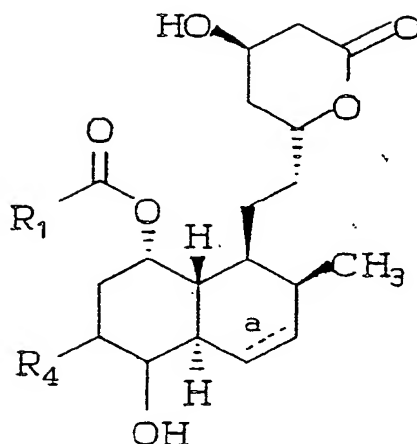
- (l) di(C₁₋₅ alkyl)amino,
 (m) phenylamino,
 (n) substituted phenylamino in which the substituents are X and Y;
 (o) phenyl C₁₋₅ alkylamino,
 5 (p) substituted phenyl C₁₋₅ alkylamino in which the substituents are X and Y,
 (q) C₃₋₈ cycloalkyl,
 (r) phenyl,
 (s) substituted phenyl in which the substituents are X and Y,
 (t) phenylS(O)_n,
 10 (u) substituted phenyl S(O)_n in which the substituents are X and Y,
 (v) phenyl C₁₋₅ alkyl S(O)_n,
 (w) C₁₋₅ alkylS(O)_n,
 (x) phenylaminoacyloxy,
 (y) C₁₋₅ alkylaminoacyloxy,
 15 (z) C₁₋₅ alkylacylamino,
 (aa) di(phenylC₁₋₅ alkyl)phosphonyl
 (bb) di(C₁₋₅ alkyl)phosphinyl
 (4) R₄ together with the carbon atom to which it is attached represents a C₃₋₈ carbocyclic ring;
 X and Y are independently selected from:
 20 a) OH;
 b) halogen,
 c) trifluoromethyl,
 d) C₁₋₃alkoxy,
 e) C₁₋₃alkylcarbonyloxy,
 25 f) phenylcarbonyloxy,
 g) C₁₋₃alkoxycarbonyl,
 h) phenyloxy carbonyl,
 i) hydrogen,
 j) C₁₋₅alkyl;
 30 T is H, tert-butyldimethylsilyl, tert-butyl diphenylsilyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, or
 tetrahydropyranyl;
 halogen is Cl or F;
a is a single bond or a double bond; which comprises treatment of a compound



(1-5)

55

with sodium borohydride to form compound (1-6); and optionally where T is not H, removal of the hydroxyl protecting group by treatment with tetrabutyl ammonium fluoride and acetic acid to form a compound



(1-6)

wherein:

R_4 is R'_4 where T is H.

2. A process according to Claim 1 wherein:

R'_4 is;

(1) hydrogen;

(2) C_{1-10} alkyl;

(3) substituted C_{1-10} alkyl in which one or more substituents is selected from:

(a) halogen,

(b) OT,

(c) amino;

(4) CH_2R_{12} in which R_{12} is selected from:

(a) C_{1-5} alkoxy,

(b) C_{1-5} alkoxy carbonyl,

(c) C_{1-5} alkylacyloxy,

(d) phenylacyloxy,

(e) phenoxy carbonyl,

(f) phenyl C_{1-5} alkyl,

(g) phenyl C_{1-5} alkoxy

(h) C_{1-5} alkylamino,

(i) di(C_{1-5} alkyl)amino,

(j) phenylamino,

(k) substituted phenylamino in which the substituents are X and Y,

(l) phenyl C_{1-5} alkylamino,

(m) substituted phenyl C_{1-5} alkyl amino in which the substituents are X and Y,

(n) C_{3-8} cycloalkyl,

(o) phenyl,

(p) substituted phenyl in which the substituents are X and Y,

(q) phenyl $S(O)_n$

(r) substituted phenyl $S(O)_n$ in which the substituents are X and Y,

(s) phenyl C_{1-5} alkyl $S(O)_n$,

(t) C_{1-5} alkyl $S(O)_n$,

(u) phenylaminoacyloxy,

(v) C_{1-5} alkylaminoacyloxy,

(w) C_{1-5} alkylacylamino,

(x) di(phenyl C_{1-5} alkyl)phosphonyl,

(y) di(C_{1-5} alkyl)phosphinyl;

(5) R'_4 together with the carbon atom to which it is attached represents a cyclopropane ring;

X and Y are independently selected from:

- a) OH,
- b) F,
- c) trifluoromethyl,
- 5 d) C₁₋₃alkoxy,
- e) hydrogen,
- f) C₁₋₅alkyl.

3. A process according to Claim 2 wherein:

R₁ is C₁₋₁₀alkyl; and

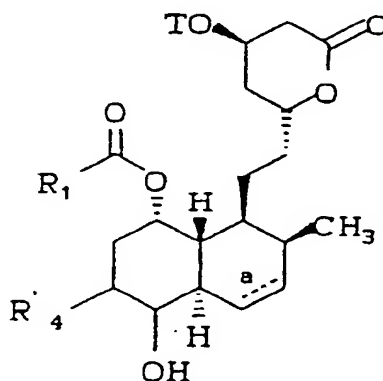
10 R₄ is CH₃, H, CH₂phenyl, or CH₂OT.

4. A process according to Claim 3 wherein:

R₁ is 2-butyl or 2-methyl-2-butyl;

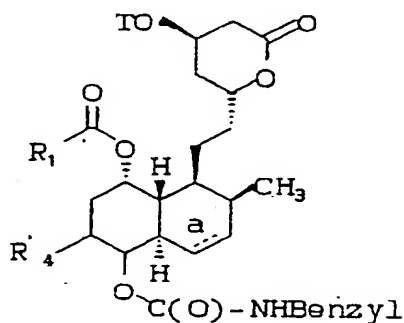
R₄ is CH₃.

5. A process of Claim 1 which further comprises treatment of compound (1-6);



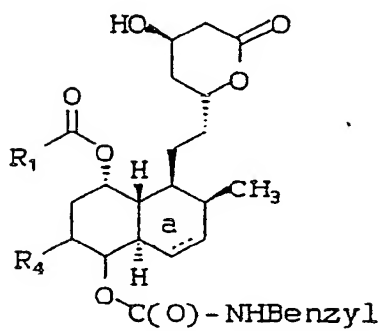
(1-6)

with benzyl isocyanate to form a compound (1-7)



(1-7)

and optionally where T is not H, removal of the hydroxyl protecting group by treatment with tetrabutyl ammonium fluoride and acetic acid to form a compound (1-7)

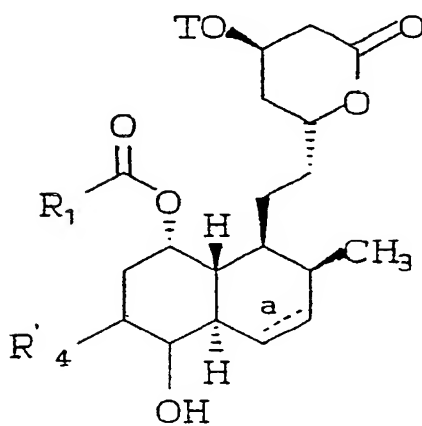


(I-7)

wherein:

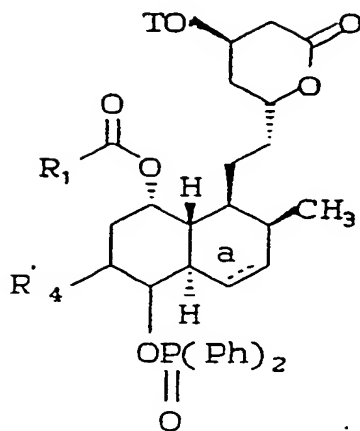
R₄ is R'₄ where T is H.

6. A process of Claim 1 which further comprises treatment of compound (106)



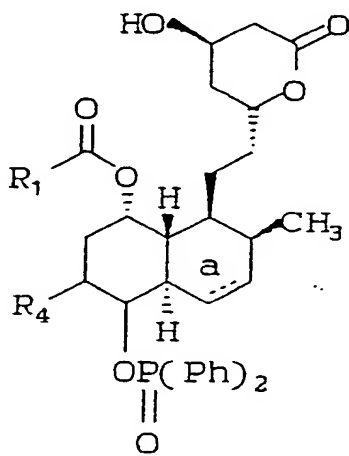
(1-6)

with diphenylphosphinic chloride (Ph₂POCl) to form a compound (1-8)



(1-8)

20 and optionally where T is not H removal of the hydroxyl protecting group by treatment with tetrabutyl ammonium fluoride and acetic acid to form a compound (I-8)

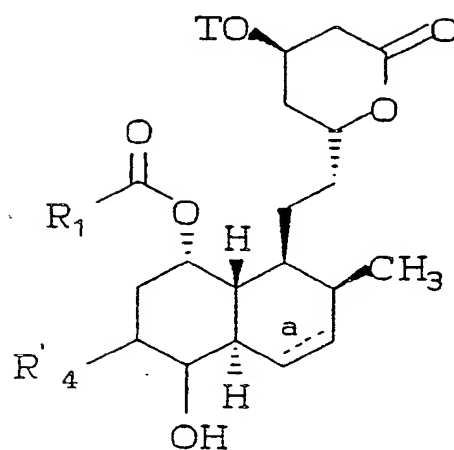


(I-8)

wherein:

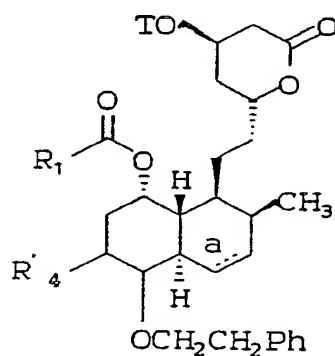
R_4 is R'_4 where T is H .

45 7. A process of Claim 1 which further comprises treatment of compound (1-6)



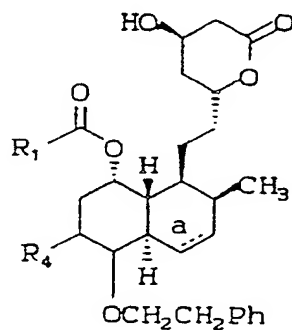
(1-6)

with β -methoxystyrene followed by hydrogenation to form a compound (1-9)



(1-9)

and optionally where T is not H, removal of the hydroxy protecting group by treatment with tetrabutyl ammonium fluoride and acetic acid to form a compound (I-9)

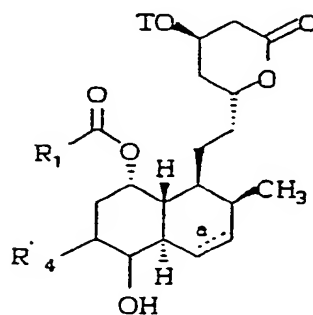


(I-9)

wherein:

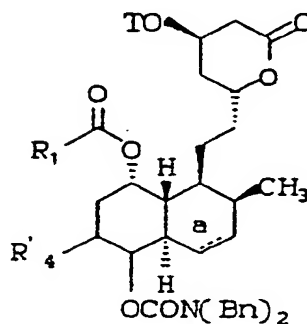
R_4 is R'_4 where T is H.

8. A process of Claim 1 which further comprises treatment of compound (1-6)



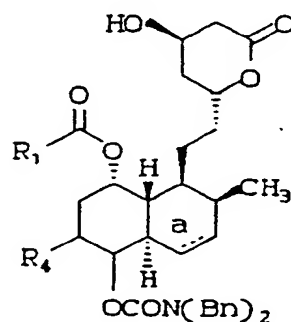
(1-6)

with phosgene followed by dibenzylamine to form a compound (1-10)



(1-10)

and optionally where T is not H, removal of the hydroxyl protecting group by treatment with tetrabutyl ammonium fluoride and acetic acid to form a compound (I-10)



(I-10)

wherein:

R_4 is R'_4 where T is H.



(9)



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

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A3

(12)

EUROPEAN PATENT APPLICATION

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(51) Int. Cl.⁵: **C07D 309/30** , **C07C 69/757** ,
A61K 31/365 , **A61K 31/22**

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(53) Date of publication of application:
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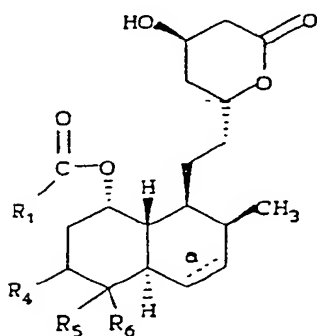
(54) Designated Contracting States:
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(58) Date of deferred publication of the search report:
09.05.90 Bulletin 90/19

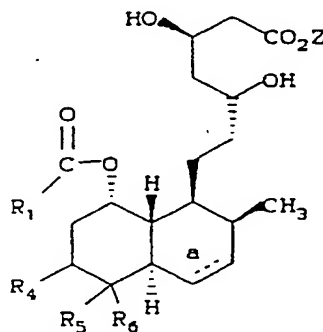
(74) Representative: **Hesketh, Alan, Dr. et al**
European Patent Department Merck & Co.,
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Harlow Essex, CM20 2QR(GB)

(54) 5-oxygenated HMG-CoA reductase inhibitors.

(57) Novel HMG-CoA reductase inhibitors are useful as antihypercholesterolemic agents and are represented by structural formulae (I) or (II):



(I)



(II)

wherein position 5 of the polyhydronaphthyl ring is singly or doubly bonded to oxygen or incorporated into a C₃₋₇ carbocyclic ring.

EP 0 349 063 A3



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 20 1642

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	DERWENT JAPANESE PATENT REPORT, vol. '9, no. 45 (C-268)[1768], 26th February 1985; & JP-A-59 186 972 (SUNTORY K.K.) 23-10-1984 * Abstract * -----	1	C 07 D 309/30 C 07 C 69/757 A 61 K 31/365 A 61 K 31/22
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 309/00 C 07 C 69/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 10-02-1990	Examiner FRANCOIS J.C.L.
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